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739.

A TREATISE ON MATERIA MEDICA AND THERAPEUTICS

R. GHOSH

FOURTEENTH EDITION

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A TREATISE ON
MATERIA MEDICA AND THERAPEUTICS

INCLUDING PHARMACY, DISPENSING, PHARMACOLOGY AND ADMINISTRATION OF DRUGS

BY THE LATE
RAKHALDAS GHOSH

FOURTEENTH EDITION

BY

BIRENDRA NATH GHOSH
F.R.F.P. & S. (Glas.)

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CALCUTTA: HILTON & CO.
1936

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PREFACE TO THE FOURTEENTH EDITION

PHARMACOLOGY is a progressive science, and with the introduction of improved methods of animal experimentation, has made enormous advances within the last thirty years. Professor Cushny and Professor Dixon will always be remembered as pioneers amongst the English Pharmacologists, and although they are not with us to-day they have left a valuable legacy of their work to serve as an impetus to future workers.

While the progress of pharmacology since the publication of the last edition has not been of such a nature as to require drastic changes, it has nevertheless been such as necessitated rewriting certain portions, and modifying a few others, to incorporate all recent advances. Moreover, the issue of a new edition of the British Pharmaceutical Codex has enabled me to introduce some of the new additions and to alter the composition of a few other preparations.

Drugs which required extensive revision are Iron, General Anæsthetics, Opium, Barbiturates, Digitalis, Anterior Pituitary, Ergot, Quinine, and the Vitamins ; while the following drugs have been for the first time discussed in this edition, *viz.* Thallium, Myocrisin, Eukodal, Dilaudide, Dicodide, Evipan, Sodium Evipan, Soneryl Sodium, Bulbocapnine, Harmine, Percaine, Gavano, Coramine, Carditone, Manganese Butyrate, Synthalin, Neptal, Carbarsone, Vioform, Antivenom Serum and Pertussis Vaccine.

The general arrangement of the book has also been modified. The section on "Pharmacy and Dispensing" has been placed at the end ; Acids have been discussed after the Alkalies ; Iron is considered with Liver Extract and Desiccated Stomach under "Drugs acting on the Blood." Quinine and other anti-malarial remedies ; Mercury, Bismuth, Arsenic and Iodides ; Antimony ; and the amœbicidal remedies, are all grouped together under "Chemotherapeutic Agents." Considering the part played by the Reticulo-endothelial System in the role of chemotherapy and immunology, a short description of this system has been given prefacing this section.

In the last edition a few diagrams were first introduced to explain the physiological principles underlying the action of drugs, some more have been added in this edition which mostly illustrate the action of drugs on animals.

While more attention has been paid to the description of pharmacology to enable the student to appreciate the rational basis of therapeutics, it is unfortunate that a proper application of this knowledge in practical therapeutics is

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lacking. It has to be admitted that while a student, or for that matter a junior practitioner, may possess a knowledge of modern pharmacology, he is incapable of writing a prescription free from incompatibles and based on rational principles, with the result that he has recourse to the use of set prescriptions or proprietary remedies of questionable value. This state of affairs, I am afraid, is noticeable almost everywhere, and to my mind is the result of teaching pharmacology not as an applied subject but as a separate subject detached from therapeutics. Moreover, while greater attention is being given to the teaching of pharmacology as a scientific subject, pure and simple, the study of Materia Medica has been neglected. The whole subject, from the point of view of teaching, requires re-adjustment on the basis of the experience gained during the past few years.

The book is issued in an enlarged form with larger types, and although the old title "Materia Medica and Therapeutics" is retained, it is now more a work on pharmacology as applied to therapeutics.

In the preparation of this edition I have received valuable help from many of my friends, and I am specially grateful to Lt. Col. J. Taylor, D.S.O., M.D., I.M.S., Director, Central Research Institute, Kasauli, for revising the section on Vaccine and Serum Therapeutics, and to Sir Hassan Suhrawardy, Kt., O.B.E., M.D., LL.D., D.Sc., etc., formerly Vice-chancellor of the Calcutta University, for much valuable help and advice.

I am also indebted to Dr. C. C. Datta, Assistant Professor of Pharmacology, Carmichael Medical College, for the help received from him in revising the proofs.

CALCUTTA
June, 1936

B. N. GHOSH

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MATERIA MEDICA

PART I

MATERIA MEDICA in its widest sense, means the description of *materials or agents* employed in the treatment of disease. But properly speaking, it includes the following branches :—

1. **Materia Medica Proper** is the science which treats of the natural history, as well as physical and chemical characters, of drugs. The term **Pharmacognosy** is used as a synonym to Materia Medica Proper.

2. **Pharmacy** is the science and art of preparing and combining drugs, so as to make them fit for administration. It can be divided again as follows :—

(*a*) **Extemporaneous Pharmacy** is the making up or the compounding of formulæ or prescriptions of medical practitioners. **Dispensing** refers to the mode of putting up, labelling, and despatching.

(*b*) **Official Pharmacy** consists in the preparation of drugs and formulæ according to such processes as are recognised by, or prescribed in, an official pharmacopœia. The **British Pharmacopœia** is the official Pharmacopœia of the British Empire.

3. **Pharmacology** is the science which describes the action of drugs on the general system, or on the individual parts of the body, in health. **Pharmacodynamics** is but another name for Pharmacology. It has been the custom of late to use the term Pharmacology in the same wide sense as Materia Medica was formerly used.

Toxicology or the toxic action of drugs comes under Pharmacology. It treats of the actions of drugs when given in doses large enough to endanger life.

4. **Therapeutics** relates to the remedial measures employed in the treatment of disease. It may be either **empirical or rational.**

(*a*) **Empirical Therapeutics** means the treatment of disease from experience only, and conforms to no pharmacological law yet known. In empirical treatment no explanation can be given for the success or otherwise of the use of a *particular drug* for a *particular disease*. We merely prescribe a certain drug because it has been found successful

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in a certain disease. A familiar example is the use of colchicum in gout. With our improved knowledge on the action of drugs and the pathology of the diseases, we can explain the actions of many drugs that were used empirically before. Thus, we can explain the action of mercury in syphilis which was formerly used purely empirically.

(*b*) **Rational Therapeutics.**—By rational treatment we mean a mode of treatment suggested by our knowledge of the chemistry, physiology, pathology and pharmacology of a given drug. Thus, when we prescribe $\frac{1}{100}$ gr. of atropine sulphate to check the night-sweats of phthisis we can explain (*see* Belladonna) how the perspiration is controlled. The use of chloral hydrate for checking tetanic convulsions, and of digitalis for the cure of cardiac dropsies, are other instances of rational therapeutics.

Accessory Therapeutics.—By accessory therapeutics is meant the treatment of disease, not by administration of drugs, but by other methods; such as, change of climate, regulation of food, clothing, exercise, baths, massage, and the like.

Chemotherapy.—Pharmacology is concerned with the physiological action of drugs and forms only a basis for the relief of symptoms rather than the cure of disease. Drugs like digitalis, adrenaline, pituitrin, etc., do not remove the underlying causes of the disease, although by relieving some urgent symptoms they remove the cause of distress and often act as curative agents. It is however in cases of diseases caused by micro-organisms or other parasites, that drugs may act purely as curative agents, and this specific treatment of infection by artificial remedies is known as *chemotherapy*, *e. g.*, treatment of syphilis by organic arsenic preparations, of amœbic dysentery by emetine, and of malaria by quinine. The term was originally used by Ehrlich to mean parasiticidal treatment of infections by chemical agents. Since certain dyes are able to stain specifically certain cellular elements, a search was made to find substances which would unite with and destroy the parasitic agents of the disease without injuring the cells of the body, *i.e.*, possess a maximum parasitotropic effect and a minimum organotropic property. But substances which are toxic to the parasites are also to a certain degree toxic to the body tissues. The object of chemotheraphy, therefore, is to find substances which the tissues will stand in large doses, but will be fatal to the infecting organism in small doses, *i.e.*, will have a favourable chemotherapeutic index, which is

$$\frac{\text{maximum tolerated dose}}{\text{minimum curative dose}}$$

The greater the index, the greater will be its value.

This specific action was supposed to be due to the selective affinity of the drug to combine chemically with the

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protoplasm of the parasite much in the same way as the binding of the toxin. Further work in this direction has shown that the action is not so simple, although it is possible that some may act as direct poison to the parasites. There are, however, quite a large number of remedies whose action cannot be explained as being directly parasitotropic.

It is possible that the co-operation of the tissues of the host is an important factor, and as will be seen later, the hydrogen-ion-concentration of the particular tissue also plays an important role in connection with the specificity of the compound.

With the growth of our knowledge regarding the causation of the different infections and the progress of synthetic chemistry, newer remedies are being daily introduced which give promising results, so that remedies which were classed as specifics cease to be so in the presence of the many newer drugs which approach more towards specific action. In fact, the word specific is used to mean that a particular preparation is more toxic to one particular parasite than on another, or nearly related one.

MATERIA MEDICA PROPER

Drugs

By "crude drugs" are meant the commercial forms of the animal or vegetable drugs as are brought to the market and utilised for the preparation of different medicinal products. Their value depends upon the presence of more or less definite chemical bodies known as "active constituents." These constituents are found in different parts of the plant, so that that particular part is used as the crude drug. Sometimes, however, they are found in all parts of the plant. In other instances no part of the plant is used as crude drug; for instance *aloe*, where the juice of the leaves contains the active constituent and forms the crude drug.

A. **Source.**—Drugs may be divided, according to their source, into the following groups :—

1. *Inorganic.*—As sulphur, mineral acids, ammonia, etc.
2. *Metallic.*—As iron, copper, silver, zinc, etc.
3. *Organic.*—(*a*) From the *vegetable kingdom*, and (*b*) from the *animal kingdom*.
4. *Synthetic.*—As chloroform, chloral, ether, amyl nitrite, etc. Some of these drugs are gradually replacing organic ones; thus the synthetic salicylic acid is being used for the natural salicylic acid derived from the oil of wintergreen.

B. **Habitat.**—By habitat is meant the natural abode or locality of a plant or animal from which a drug is obtained.

C. **Collection.**—The medicinal activity of a drug depends greatly upon the habitat and the season of the year when it

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is gathered. Thus, rhubarb is useless until it is six years old. China and Turkey rhubarb are richer than those grown in India. The old cinchona bark is richer in quinine than the new.

COMPOSITION OF DRUGS

Inorganic drugs have a definite composition, which is well expressed by their names and chemical formulæ. The composition of organic drugs on the other hand, is always complex and is ascertained after considerable analytical labour. They consist chiefly of acids, bases, salts, albuminous substances, alkaloids, balsams, cellulose, colouring matters, extractive matters, ferments, glycosides, gums, gum-resins, neutral principles, fixed and volatile oils, oleo-resins, starch, sugar, etc. Some of them require a brief explanation.

Alkaloids are the active nitrogenous principles formed for the most part in the tissues of plants or animals. They may occasionally be prepared synthetically. According to Hale White, their characteristics are as follows :—

"(1) They are the active nitrogenous principles of organic bodies.

"(2) They are compound ammonias; that is to say, one or more atoms of hydrogen in ammonia (NH_3) are replaced by various radicals.

"(3) They combine with acids to form crystalline salts without the production of water.

"(4) They are alkaline, turning red litmus paper blue.

"(5) A few are liquid, such as pilocarpine, coniine, nicotine, sparteine, lobeline. Liquid alkaloids nearly always contain only carbon, hydrogen and nitrogen.

"(6) The solid ones are colourless, crystalline, and contain oxygen.

"(7) They are sparingly soluble in water, readily so in alcohol. The salts are usually soluble in water.

"(8) The solutions of many are intensely bitter.

"(9) Most of them are closely related to pyridine, and some may be synthetically prepared from pyridine bases."

The following alkaloids or their salts are official :—

Atropine	Codeine	Physostigmine
Caffeine	Morphine	Quinine
Cocaine	Pilocarpine	Strychnine

It should be noted that the names of alkaloids in Latin terminate in *ina*, and in English *ine*. As *Atropina* (Latin), *Atropine* (English).

Vegetable alkaloids occur in almost all parts of plants, but are most abundant in the seeds and roots, especially of dicotyledonous plants. A few are found in the lower plants, *e.g.*, *muscarine* and *ergotoxine*. *Bases* found in the animal

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kingdom are commonly known as leukomains and ptomains. The former are produced by the body cells and are products of metabolism, *e.g.*, *adrenaline*, while the latter result from microbic decomposition of dead material, especially the amino-acids. These *bases* are known as **amines**, and are derived from ammonia by replacing H by alkyl groups.

Some plants contain many alkaloids, *e.g.*, cinchona, in others one alkaloid is found in one part of the plant and another in a different part of the same plant.

Alkaloids are also prepared artificially, *e.g.*, theophylline, suprarenin.

Incompatibles.—(*a*) *Alkalies*, which precipitate the less soluble pure alkaloid.

(*b*) *Tannin*, forming insoluble tannates.

(*c*) *Iodides* and *bromides*, forming insoluble iodides or bromides, or double salts, etc.

(*d*) *Mercuric chloride*, forming insoluble double salt.

Acids are salts of hydrogen. Numerous organic acids are found in plants, either in combination with inorganic bases such as potassium or calcium, or in a free state.

Bases are substances which react with acids and form salts. They are of two kinds:—(*a*) *Elementary*, to which metals belong. (*b*) *Compound*, such as ammonium and the alkaloids.

Glycosides are colourless crystalline solids soluble in water and alcohol. They split up on hydrolysis into a reducing sugar and a non-sugar component called *aglucone*. They are found in plants and liberate sugar with acids and certain ferments. They are neutral or weakly acid, and contain carbon, hydrogen and oxygen, a few have nitrogen in addition, and one or two, sulphur. They differ greatly in their solubility in water and alcohol, being mostly insoluble in ether. Some are powerful poisons while others are almost inert. Most of these are lævorotatory and have slightly bitter taste. Salicin, jalapin, digitalin, digitoxin, senegin, strophanthin, glycyrrhizin, are some of the glycosides. The term *glucoside* is applied only to those glycosides in which the sugar component is glucose.

Tannins are substances found in many plants specially in the leaves and bark. They are non-nitrogenous. Some are glycosides and form a group of phenol derivatives. They are soluble in alcohol and water, have an astringent taste and give a bluish or greenish colour with iron salts. They are precipitated by lead acetate, albumin and alkaloids.

Saponins are non-nitrogenous substances generally glycosides, which emulsify oils and lake red blood-cells. On hydrolysis they yield sugar and a non-sugar component—*sapogenin*. They are neutral in reaction and form froth when mixed with water. The toxic ones are known as **sapotoxins**.

Neutral principles are indifferent crystalline proximate principles whose chemical composition is not known. They

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resemble alkaloids in action. As aloin, santonin, picrotoxin, quassin, etc. Many of them have a bitter taste, as quassin, and are called "*amroids or bitter principles.*"

Note.—Whereas the names of all alkaloids end in "*ine,*" those of glycosides and neutral principles end in "*in.*"

Balsams.—These are oleo-resins or resins containing either benzoic or cinnamic acid or both. *Benzoin, balsam of Peru* and *tolu, prepared storax,* are the balsams of the B.P. Copaiba and Canada balsam do not come under this group, though they are named balsams.

Oils of different kinds are used in medicine for a variety of purposes. They are fixed, and volatile.

A. **Fixed Oils** and **Fats** are mixtures of olein (liquid), palmitin (semisolid), and stearin (solid), with a small amount of other bodies in addition. They are found mostly in seeds, occurring within the cells as drops or crystals. They are insoluble in water, sparingly soluble in alcohol, freely in ether and chloroform, benzol, carbon disulphide and turpentine. With alkalies they form soap and glycerin, *e.g.*, castile soap, which is made by the action of sodium hydroxide on olive oil, which is practically pure olein, thus :—

$$\underset{\substack{\text{Oleate of Glyceryl}\\ \text{or Olein}\\ \text{(Vegetable Oil)}}}{C_3H_5(C_{18}H_{33}O_2)_3} + \underset{\substack{\text{(Caustic}\\ \text{Soda)}}}{3NaOH} = \underset{\substack{\text{Hydrate of}\\ \text{Glyceryl}\\ \text{(Glycerin)}}}{C_3H_5(OH)_3} + \underset{\substack{\text{Oleate of Sodium}\\ \text{(Hard Soap)}}}{3NaC_{18}H_{33}O_2}.$$

Fats are fixed oils which remain solid at ordinary temperature, but differ from oils in the relative proportion of these basal ingredients, the fats having more of the stearin and palmitin, making them solid or semisolid, and the oils more of the liquid olein.

Characters of fixed oils :—

(*a*) non-volatile, and so leave a permanent grease spot;

(*b*) they cannot be distilled;

(*c*) under the influence of heat decompose and become rancid;

(*d*) they are almost bland non-irritating substances (except croton oil) with nutrient and emollient properties; and

(*e*) they form soaps with alkalies.

A few of the fats and oils are of animal origin, *e.g.*, butter, lard, suet and cod-liver oil, but the majority are of vegetable origin, as almond, linseed, olive and castor oils, and cocoa butter.

Castor oil and croton oil differ from the others in being soluble in alcohol and in possessing cathartic properties.

The *mineral oils* do not belong to the class of organic drugs. They are petroleum products, being mixtures of hydrocarbons, and do not become rancid.

Waxes are of firmer consistence than the fats, have a higher melting point, and cannot be saponified by boiling with an alkali.

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B. **Volatile Oils.**—As plants often owe their characteristic odour to these oils they are often spoken of as *essential oils.* They contain a large number of preparations of diverse character and action. They are obtained by a process of distillation, except lemon oil, which is obtained by expression. They are found chiefly in the fruits and flowering parts of plants, or in the seeds and leaves. Owing to their strong characteristic odours they are largely used in perfumery, and to cover the taste and smell of nauseous drugs. As a rule they are clear, colourless liquids; some like cajuput and cubebs have peculiar greenish colour; cade, dark reddish-brown; and croton oil brownish yellow. Oil of cinnamon when old becomes reddish-brown. The commonest constituents are terpenes, sesquiterpenes and a few diterpenes. Terpenes are hydrocarbons of the aromatic series. In addition, they contain oxidised aromatic substances, as phenols and their derivatives, aromatic alchols of the benzene series, and their corresponding aldehydes and ketones, aromatic alcohols of the camphor series, and sesquiterpene alcohol.

(*a*) They are volatile and can be distilled, and do not leave a permanent grease spot.

(*b*) They do not form soaps with alkalies.

(*c*) They do not become rancid, but tend to resinify on exposure to light and air; and

(*d*) They are sufficiently soluble in water to impart to it their taste and odour.

Some of the volatile oils which are non-existent in the living plants are formed either by destructive distillation, or by the action of ferments on glycosides in the presence of water. The former are spoken of as **Empyreumatic Oils.**

Bastedo has conveniently grouped the volatile oils as follows:—

A. Existing in plant as such	1. Terpenes, $C_x H_x$ (oils of turpentine, juniper, etc.). 2. Terpenes + stearoptenes (oils of lemon, peppermint, etc.).
B. Not existing in plant as such, but developed from plant constituents	3. From enzyme action (oil of mustard). 4. Empyreumatic oils (oil of cade, oil of tar, creosote).

In group 2 we have the mixtures of terpenes holding in solution oxygenated bodies of variable chemical nature. The terpene portion is known as *eleoptene*, the oxygenated portion as *stearoptene.* This stearoptene can be separated from the eleoptene by cold or fractional distillation, and is usually solid. They are therefore oxidised hydrocarbons of a crystalline nature, or solid volatile oils. The best known examples of stearoptenes are camphor, menthol and thymol.

Lipoids, Lipins or **Lipides.**—These are a group of substances resembling fats in their solubility in ether, alcohol,

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etc. They are widely distributed in the animal tissues chiefly nervous tissues. Lecithin and cholesterol are of interest to us.

Gums are colloidal carbohydrates which swelling or dissolving in water form viscid adhesive fluids known as *mucilage*. They are exudations from the stems, or branches, or both, of plants, and are composed of

(1) *Arabin*, soluble in water ; as gum arabic.
(2) *Bassorin*, partially soluble in water ; as tragacanth.
(3) *Cerasin*, or insoluble gum.

Pectin or vegetable jelly occurs in some medicinal plants and is allied to gum.

Resins are solid, brittle, non-volatile complex substances derived from the oxidation of volatile oils. They are soluble in alkalies forming resin soaps, and in alcohol, but insoluble in water. The resins of the B. P. are colophony, scammony, and podophyllin. When they are found dissolved in volatile oils they are known as **oleo-resins**, *e.g.*, copaiba, canada turpentine. Sometimes they are found in combination with gums and volatile oils, and are then known as **gum-resins**. They form emulsions when mixed with water. Ammoniacum and asafetida are examples of gum-resins.

Salts are compounds of acids and bases.

IMPURITIES OF DRUGS

1. **Imperfect Selection.**—This is due to the ignorance of collectors of crude vegetable drugs, who are imperfectly acquainted with their botanical characters and therefore fail to distinguish them from allied species; hence the substitution of an inferior or allied article for the genuine one.

2. **Imperfect Preservation** is one of the causes of deterioration of many drugs. Several drugs are materially affected by light and air, others by the lapse of time. Deliquescent salts and scale iron preparations quickly undergo physical change unless they are kept in carefully stoppered bottles. Syrupus Ferri Iodidi and Easton's Syrup are decomposed by light. Ergot, unless carefully dried and packed in an air-tight receptacle, soon becomes mouldy and loses strength. All extracts deteriorate unless put securely in sealed pots.

3. **Imperfect Preparation.**—Impurities are of two kinds, *(a)* those which exist in the crude drug, *(b)* those which arise as by-products during the process of manufacture. They can be avoided only by scrupulous care on the part of the manufacturing pharmacist.

4. **Adulteration** is the intentional and fraudulent admixture of foreign substances with a drug. All highly priced drugs are liable to adulteration. Quinine is often adulterated, and Murrell mentions that once a large consignment of quinine was sent out to India containing not a trace of cinchona alkaloids.

THE BRITISH PHARMACOPŒIA AND PHARMACEUTICAL PROCESSES

By a Pharmacopœia is meant a book published under the authority of a recognised body, generally constituted by law, for the purpose of securing uniformity of composition and strength of medicines used in the treatment of disease. The

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General Medical Council of the United Kingdom, authorised by the Medical Act of 1858, issues and revises from time to time the British Pharmacopœia. The first B. P. was published in 1864, and the last in 1932. One of the principal changes in the present edition is the introduction of the Metric System in the place of Imperial weights and measures. Other countries, as the United States, Germany, France, etc., also publish their own Pharmacopœias. Even hospitals have their own special pharmacopœias for speedy dispensing. Although the B.P. is the legal standard, no medical man is bound to follow it. Drugs and preparations contained in the British Pharmacopœia are known as *official*.

The Council of the Pharmaceutical Society of Great Britain periodically publish a book called "The British Pharmaceutical Codex" which contains not only all the drugs and preparations of the British Pharmacopœia but also many other preparations not contained in it. The abbreviation of the British Pharmaceutical Codex is B.P.C.

The following pharmaceutical processess are generally used :—

Bruising or **Contusion** is the process by which tough, hard and woody, soft, elastic and juicy substances are smashed or broken up in a roller-mill, or disintegrator, or on a small scale, in an iron mortar, so as to reduce them to a form suitable for being acted upon by a solvent, either by maceration, infusion, or decoction.

Calcination or **Incineration** is the operation by which drugs are exposed to a high temperature in order that watery and volatile matters may be driven off. This is best effected by putting the drugs in a crucible over a furnace.

Crystallisation is the process by which substances are made to assume the form of crystals.

Decoloration is the process by which we remove the colouring matters from alkaloidal substances, such as atropine, morphine, etc. This is effected by treating their solutions or mixtures with dried and purified animal charcoal, and subsequent filtration.

Despumation is the process by which an organic fluid is boiled until the impurities rise to the surface as scum, which is then removed by skimming or straining. Syrups made by this process keep longer.

Dialysis is the process of separating crystalloids from colloids by passing them through an animal membrane.

Digestion is a prolonged maceration at a temperature higher than that of the air.

Elutriation is the process by which a substance is pulverised and mixed with water, the coarser grains falling down to the bottom, while the lighter and finer ones are poured off with the water into another vessel, where deposition takes place slowly.

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Expression is the process by which we press out juices and oils from vegetable substances, as in the preparation of succi, or squeeze out the liquid from the marc as in the preparation of tinctures. For this process suitable presses are required.

Fusion, Liquefaction or **Melting** is the process by which we melt or liquefy any solid body by heat. This is effected by putting it into a suitable vessel or crucible over a heated furnace, or on a water, steam or sand bath. We employ this process in the preparation of plasters, ointments, suppositories, caustic sticks, etc.

Granulation is the process by which a coarsely crystalline salt is converted into a granular powder by dissolving the former in water, and evaporating the solution to dryness with continuous stirring. Carbonate and citrate of potassium are made in this way.

Levigation is the pulverisation of a solid in the presence of water, or any other liquid which does not dissolve it; the finely comminuted particles being gathered with the washings and allowed to deposit slowly, whilst the coarser particles are again ground with the water or liquid, and so on, until the whole of the solid is reduced to a condition of fine powder.

Lixiviation means the separation of a soluble salt, from a mixed or compound solid, by dissolving the latter in water, decanting the supernatant liquid into another vessel, and evaporating it to dryness, leaving the insoluble residue behind. The solution is called a "*Lye.*"

Maceration is the process of steeping a substance in alcohol, or some similar menstruum without the application of heat, in order to dissolve out its soluble matters. The insoluble residue is called the "*marc.*"

Percolation is the process of extracting soluble matters by filtration of a liquid menstruum through a porous column of powdered material. A special apparatus, called a Percolator, is required.

Scaling is the process by which the scale preparations of drugs are made. It consists in spreading out in a thin layer, the concentrated solution of a drug on a glass, and allowing it to dry. The dried film is then separated and broken up. The scale iron preparations are made by this process.

Sifting is the method by which we separate finer powders from coarser ones, by means of a sieve, which is made of either wire, horse-hair or muslin, of varying degrees of closeness. The B.P. directs a drug in No. 10, 22, 44, 60 or 85 powder, and thereby means a degree of disintegration, as represented by the number of parallel wires in either transverse direction contained within the linear inch of a sieve.

When the soft pulp of fruits like figs, baels, prunes or tamarinds is required to be sifted, the operation is called

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"**pulping**" which requires a great force in squeezing the pulp through the sieve.

Sublimation is the operation by which a solid is first vaporised by heat, and then the vapour is condensed as a deposit on the surface of another vessel, either *en masse*, in which case it is called a **sublimate**, as corrosive sublimate, or in a small feathery pulverulent state, known as flowers, as flowers of sulphur.

WEIGHTS AND MEASURES OF THE BRITISH PHARMACOPŒIA

METRIC SYSTEM

Measures of Mass (Weights)

1 Kilogram (kg. or kilog.) is the Standard or International Kilogram
1 Gramme (grm.) = the 1000th part of 1 kilogram
1 Milligram (mg.) = the 1000th part of 1 gramme

For the purpose of writing prescriptions, in order to avoid the possibility of confusion between 'gramme' and 'grain', the symbol 'G.' should be used as the contraction for 'gramme'.

Measures of Capacity (Volumes)

1 Litre (lit.) is the volume occupied by the mass of 1 kilogram of water at the temperature of its maximum density.
1 Millilitre or Mil (mil.) = the 1000th part of 1 litre.

1 litre measures about 1000.028 cubic centimetres.

Measures of Length

1 Metre (m.) is the Standard or International Metre
1 Centimetre (cm.) = the 100th part of 1 metre
1 Millimetre (mm.) = the 1000th part of 1 metre
1 Micron (μ) = the 1000th part of 1 millimetre

IMPERIAL SYSTEM

Measures of Mass (Weights)

1 Pound (Avoir.) (lb.) is the Standard Pound as defined in the Weights and Measures Act, 1878, Section 13

1 Ounce (Avoir.) (oz.) = the 16th part of 1 pound = 437.5 grains
1 Grain (gr.) = the 7000th part of 1 pound

Measures of Capacity (Volumes)

1 Pint (pt.) is the Imperial Standard Pint as defined in the Weights and Measures Act, 1878, Section 15.

1 Fluid Ounce (fl. oz.) = the 20th part of 1 pint = 8 fl. dr.
1 Fluid Drachm (fl. dr.) = the 8th part of 1 fluid ounce = 60 min.
1 Minim (min.) = the 60th part of 1 fluid drachm.

Relation of Capacity to Mass (Imperial)

1 Minim = the volume at 16.7° (62° F.) of 0.9114583 gr. of water
1 Fluid Drachm = the volume at 16.7° (62° F.) of 54.6875 gr. of water
1 Fluid Ounce = the volume at 16.7° (62° F.) of 1 oz. or 437.5 gr. of water
109.7143* Minims = the volume at 16.7° (62° F.) of 100 gr. of water

* Taken as 110 minims throughout the Pharmacopœia

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In the B.P. "per cent." is used to mean the following:—
Per cent. w/w = weight in weight.
Per cent. w/v = weight in volume.
Per cent. v/v = volume in volume.

Relations of Metric and Imperial Measures

Mass

1 Kilogram	(kg. or kilog.)	=	15,432.3564 grains, or 35.274 ounces nearly, or 2.2046 pounds nearly
1 Gramme	(grm.)	=	15.4323564 grains
1 Milligram	(mg.)	=	0.015 grain nearly
1 Pound (Avoir.)	(lb.)	=	453.59 grammes nearly
1 Ounce (Avoir.)	(oz.)	=	28.350 grammes nearly
1 Grain	(gr.)	=	0.0648 gramme nearly

Capacity

1 Litre	(lit.)	=	1.75980 pints, or 35.196 fluid ounces nearly
1 Millilitre or Mil	(mil.)	=	16.9 minims nearly
1 Pint	(pt.)	=	568.2454 mils nearly, or 0.5682 litre nearly
1 Fluid Ounce	(fl. oz.)	=	28.4123 mils nearly
1 Fluid Drachm	(fl. dr.)	=	3.5515 mils nearly
1 Minim	(min.)	=	0.0592 mil nearly

Length

1 Metre	(m.)	=	39.370113 inches
1 Centimetre	(cm.)	=	0.39370 inch
1 Millimetre	(mm.)	=	0.039370 inch
1 Micron	(μ)	=	0.00003937 inch
1 Inch	(in)	=	25.3999 millimetres

TABLE OF APPROXIMATE EQUIVALANCES ADOPTED IN STATING DOSES (IMPERIAL AND METRIC) IN THE BRITISH PHARMACOPŒIA

Mils Grammes	Minims Grains	Mils Grammes	Minims Grains
10	150	0.3	5
8	120	0.25	4
6	90	0.2	3
5	75	0.15	2½
4	60	0.12	2
3	45	0.1	1½
2.6	40	0.08	1⅓
2	30	0.06	1
1.6 or 1.5	25	0.05	⅘ or ¾
1.2 or 1.3	20	0.04	⅔
1	15	0.03	½
0.8	12	0.025	⅖
0.6	10	0.02	⅓
0.5	8	0.016	¼
0.4	6	0.012	⅙

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Gramme	Grain	Gramme	Grain
.01	$\frac{1}{6}$	.001	$\frac{1}{64}$ or $\frac{1}{60}$
.008	$\frac{1}{8}$	.0008	$\frac{1}{80}$
.006	$\frac{1}{10}$	.0006	$\frac{1}{100}$
.005	$\frac{1}{12}$	.0005	$\frac{1}{120}$
.004	$\frac{1}{16}$	.0004	$\frac{1}{160}$
.003	$\frac{1}{20}$	.0003	$\frac{1}{200}$
.0025	$\frac{1}{24}$	.00025	$\frac{1}{240}$
.002	$\frac{1}{30}$	.0002	$\frac{1}{500}$ or $\frac{1}{320}$
.0015	$\frac{1}{40}$	.00015	$\frac{1}{400}$
.0012	$\frac{1}{50}$	.00012	$\frac{1}{500}$

STANDARDISATION OF DRUGS AND BIOLOGICAL ASSAY

Standardisation is the method adopted to obtain a definite uniformity in the strength of certain preparations containing active or alkaloidal principles, such as the extract of nux vomica, tincture of strophanthus, etc. This may be accomplished by chemical or pharmacological methods, generally expressed as pharmaceutical assaying. This secures a means of measuring therapeutic activity and makes it possible to furnish uniform preparations. Drugs having a definite chemical composition can be standardised by means of chemical assay. This method is also utilised for opium, belladonna, nux vomica, etc., where the active constituents can be isolated in the pure form. But quite a large number of drugs and their preparations cannot be assayed by chemical methods, either because their active ingredients are not known, or perhaps they can not be isolated quantitatively in a pure form by any chemical methods. They are assayed by biological methods. The Pharmacopœia gives details of the methods to be followed in each case, and this should be consulted. The following are the principal methods.

1. *Toxic Method.*—Guinea pigs, frogs, cats or other animals are generally selected for this test, and the value of the drug or preparation is calculated on the amount required to cause the death of the animal.

2. The amount required to produce certain definite effects on the animals, *e.g.*, cock's comb method for ergot.

3. The amount required to produce a definite effect on an isolated organ, *e.g.*, effect of pituitary extract on isolated uterus.

4. The amount required to clear the peripheral blood of mice infected with trypanosomes within 24 hours.

According to the British Pharmacopœia (1932) the following preparations are biologically assayed:—

Neoarsphenamine and **Sulpharsphenamine.**—These must comply with the test for absence of undue toxicity and for therapeutic potency.

(*a*) *Absence of undue toxicity.*—The average lethal dose of the standard preparation is 7.2 milligrams per mouse weighing from 13 to 15 grms. If the toxicity of the sample does not exceed that of the standard preparation by more than 20 p.c., it passes the test. It is tested

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by giving intravenous injection of 0.3 mil of a 2 p.c. solution of neoarsphenamine (or 0.35 mil *subcutaneously* of sulpharsphenamine) to mice weighing 13 to 15 grms. If not more than two die within three days the sample passes the test.

(*b*) *Therapeutic potency.*—This should have a curative action not less than the standard preparation kept in the National Institute for Medical Research, London. 0.03 mgrm. per grm. of body weight when injected into a vein of moderately infected mice (100,000 to 500,000 of trypanosomes per c.c. of blood) will clear the peripheral blood of trypanosomes in 48 to 72 hours.

Sulpharsphenamine is injected *subcutaneously.*

Digitalis.– The International Unit is the activity contained in 0.1 grm. of the standard digitalis powder. (1) The *frog test* consists of making injections of suitable dilutions of the extract of standard preparation and of the sample into similar groups of frogs and determining the amount of extract in mils required to produce death by systolic standstill of the ventricle per 100 grm. frog within 24 hours. The potency is calculated by comparing with that of the standard the percentage mortality amongst the frogs.

(2) *Cat or guinea-pig test* is done by slowly injecting into a vein extract of special strength into anæsthetised animals and determining the amount required to arrest the heart. The potency is determined by dividing the average lethal dose of the standard preparation by the dose required of the sample preparation.

Strophanthus and **Tincture of Strophanthus** are standardised in the same way.

Insulin.—The standard preparation is the dry soluble insulin hydrochloride, prepared and kept in the National Institute of Medical Research, and samples when injected into rabbits should produce the same percentage of reduction of blood sugar as the standard, *i.e.*, ±10 p.c.

Ten or twelve healthy rabbits, each weighing about 2000 grm., are kept without food for 20 hours preceding the test, and divided into two groups. Each rabbit of the first group gets 1 Unit of the standard preparation subcutaneously, while the second group gets 0.5 Unit of the sample to be tested. The blood sugar is estimated from the blood of each rabbit drawn at the end of each hour for five hours, and the average fall of blood sugar noted. Three or four days later the same test is repeated but the rabbits which received the standard preparation receive the test sample and the batch which received the test sample receive the standard sample, and the average 'percentage blood sugar reduction' again tested.

The sum of the numbers for the precentage of blood sugar reduction for two days with the standard sample is divided by the sum of the percentage blood sugar reduction with the test sample, and the result multiplied by hundred represents the percentage activity of the sample being tested in terms of the solution of the standard preparation.

Pituitary Extract.—The International Unit is the activity of 0.5 mgrm. of the standard acetone extracted preparation. The activity is determined from the amount of extract required to produce equivalent contraction of isolated uterus of guinea-pigs weighing 170 to 270 grms. as soon as weaned, suspended in a bath containing special oxygenated saline.

Old Tuberculin.—The potency is tested by comparing the dose necessary to produce its specific toxicity in guinea-pigs or other animals infected with the *B. tuberculosis*, with the standard preparation necessary to give the same effect. The inflammatory reaction is produced after 24 hours.

Diphtheria Antitoxin.—Its potency is determined by comparing the dose necessary to protect guinea-pigs against the effect of a fixed dose of diphtheria toxin, with the dose of standard preparation of diphtheria antitoxin, necessary to give the same protection.

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Gas-gangrene Antitoxin.—Its potency is determined by comparing the dose necessary to protect mice or other animals against the lethal effect of gas-gangrene toxin, with the dose of a standard preparation of gas-gangrene antitoxin (perfringens), necessary to give the same protection.

Anti-dysentery Serum.—The assay is done in the same way as other sera except that the standard preparation of anti-dysentery serum is used. The Unit is the specific neutralising activity for the *B. dysenteriæ* (Shiga), contained in such an amount of the standard preparation as the Medical Research Council may indicate.

Tetanus Antitoxin.—For the comparison of potency there are necessary (*a*) the standard preparation of tetanus antitoxin, and (*b*) a suitable preparation of tetanus toxin for use as a test toxin. The unit is the specific neutralising activity for tetanus toxin contained in the standard preparation. The potency of a sample is determined by comparing the dose of it, necessary to protect guinea-pigs or mice against the lethal effect of a fixed dose of tetanus toxin, with the dose of the standard preparation of tetanus antitoxin, necessary to give the same protection.

Antirachitic Vitamin D.—The activity of vitamin D is determined by comparing its antirachitic activity with the standard preparation of Great Britain and Northern Ireland, kept in the National Institute of Medical Research and is expressed in Units per gramme.

Curative Assay.—About 20 young rats, weighing 40 to 60 grms. are fed for about three weeks on rachitogenic diet * and the degree of rickets determined by taking X-ray photographs. The rats are now divided into two groups, one group receive daily doses of 0.25 unit of the standard preparation, while the other group the preparation to be tested, for 10 to 14 days. After this the rats are killed and the extent of cure of rickets is estimated by means of X-ray photographs.

Prophylactic Assay.—About 20 young rats weighing from 40 to 50 grms. are fed on one of the rachitogenic diets for 4 to 5 weeks after which they are divided into two groups. Rats of one group receive daily dose of 0.1 Unit of standard preparation, while the other receive the preparation to be tested. At the end of the period the rats are killed, and corresponding bones are taken from every rat. The weight of the ash is determined for the two groups. The average precentage of the bone ash of the rats fed on the sample to be tested, against the same of the rats fed on the standard preparation, gives the strength of the preparation tested.

OFFICIAL OR PHARMACOPŒIAL PREPARATIONS

The official preparations are sometimes called Galenical, after the celebrated physician Galen, but this term is now a misnomer, as with the advance of pharmacy, many drugs have come into use which were unknown in Galen's days.

Few drugs can be administered in their natural state. They are either too nauseous, too bulky, or, contain some principles which are injurious to life or health. They are, therefore, submitted to certain processes prescribed by the

* Rachitogenic diet.—Ground yellow maize, whole wheat, each 33 p.c.; wheat gluten, gelatin, each 15 p.c.; calcium carbonate, 3 p.c.; sodium chloride, 1 p.c., or

Ground yellow maize, 76 p.c.; wheat gluten 20 p.c.; calcium carbonate 3 p.c.; sodium chloride 1 p.c.

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British Pharmacopœia, in order to render them fit for administration, and also to help their preservation and storing, so as to maintain an uninterrupted supply during all seasons of the year. In the following pages we have given all the official preparations of the B.P. of 1932 in a tabular form, with their compositions, strengths, doses, and in many instances, their actions and uses.

Aceta.—Vinegars are solutions of drugs in acetic acid, not in Vinegar. There is only one in the B.P.

Acetum Scillæ.—Squill bruised 10 gms., acid acetic dilute 100 mils. *Dose.*—10 to 30 ms. or 0.6 to 2 mils.

Acida Diluta.—Diluted Acids are strong acids diluted with distilled water. They are seven in number :—

Acidum	Preparation	Dose	Action and uses
Aceticum Dil.	Acetic acid 182 G., water 818 G.	30 to 60 ms. 2 to 4 mls.	Refrigerant and diuretic.
Hydrobromicum Dil.	A solution containing 10 p.c. hydrogen bromide by wt.	15 to 60 ms. 1 to 4 mls.	Sedative. Prevents cinchonism.
Hydrochloricum Dil.	Hydrochloric acid 313 G., water 687 G. Contains 10 p.c. HCl.	5 to 60 ms. 0.3 to 4 ml.	Acid dyspepsia, gastric troubles.
Hydrocyanicum Dil.	A solution containing 2 p.c. of hydrogen cyanide by weight.	2 to 5 ms. 0.12 to 0.3 ml.	Sedative. A deadly poison. In vomiting, painful gastric disorders, &c.
Hypophosphorosum Dil.	Barium hypophosphite and dilute sulphuric acid. 10 p.c. hypophosph. acid.	5 to 15 ms. 0.3 to 1 mil.	
Phosphoricum Dil.	Phosphoric acid 112 G., water 888 G.	5 to 60 ms. 0.3 to 4 ml.	Tonic, refrigerant.
Sulphuricum Dil.	Sulphuric acid 104 G., water 896 G.	5 to 60 ms. 0.3 to 4 ml.	Tonic, astringent To check diarrhœa.

The dosage of all varies from **5 to 60 ms.**; except—Acid. Hydrocyanicum Dil., **2 to 5 ms.**; Acidum Hydrobromicum Dil., **15 to 60 ms.**; Acidum Hypophosphorosum Dil., **5 to 15 ms.**, and Acidum Aceticum Dil., **30 to 60 ms.**

Adeps and Adeps Lanæ. Lard and Wool Fat. Two preparations, as follows :—

Adeps Benzoinatus.—Prepared lard 1000 gms., powdered benzoin 30 gms. Melt the lard in a water-bath, mix and strain.

N.B. In India suet should be used in place of lard.

Adeps Lanæ Hydrosus. Syn.—Lanolin.—Wool fat 7 gms., distilled water 3 mils. Mix by trituration in a warm mortar.

Aquæ. Waters.—With the exception of distilled water, sterilised water, and Aq. Chloroformi all aquæ are weak and simple solutions of volatile oils obtained as described under aromatic waters. They are nine in number :—

Aqua	Preparation	Dose	Action
Anethæ Conc.	Oil of dill 2 mils., alcohol (90 p.c.) 60 mils., water q.s. to 100 mils.	5 to 15 ms. (0.3 to 1 ml.)	Carminative.
Anethæ Dest.	Dill 10 gm., water 200 ml. distil 100 mils.	½ to 1 oz. (15 to 30 ml.)	Do.
Camphoræ	Camphor 1 gm., alcohol (90 p.c.) 2 mils., and distilled water 1000 mils. By solution.	½ to 1 oz. (15 to 30 ml.)	Stimulant and antispasmodic. As a vehicle.

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Aqua	Preparation	Dose	Action
Chloroformi	Chloroform 2.5 mils., distilled water to 1000 mils by solution.	½ to 1 oz. (15 to 30 ml.)	A flavouring agent.
Cinnamomi Conc.	Cinnamon oil 20, alcohol (90 p.c.) 600, water q.s. 1000.	5 to 15 ms. (0.3 to 1 ml.)	Carminative flavouring agent.
Cinnamomi Dest.	Cinnamon bruised 1 gm. and water 20 mils., distil 10 mils.	½ to 1 oz. (15 to 30 ml.)	A carminative.
Destillata	Distilled from natural potable water.	.....	A vehicle.
Menthæ Pip. Conc.	Peppermint oil 20, alcohol (90 p.c.) 600, water q.s. 1000	5 to 15 ms. (0.3 to 1 ml.)	A vehicle. An antispasmodic and carminative vehicle.
Menthæ Pip. Dest.	Oil of peppermint 1 mil. and water 1500 mils., distil 1000 mil.	½ to 1 oz. (15 to 30 ml.)	Do.

Aquæ Aromaticæ.—**Aromatic waters** are prepared either by (*a*) *distillation*, (*b*) *solution*, *i.e.*, by shaking the essential oil with five hundred times its volume of distilled water for fifteen minutes and filtering after 12 hours ; or by triturating the oil with powdered talc, keiselguhr, or pulped filter paper, and five hundred times its volume of distilled water, and filtering ; or (*c*) by diluting the concentrated water with 39 times its volume of distilled water.

N.B.—Concentrated aromatic waters are weak alcoholic solutions of volatile oils which when diluted with 39 times its volume of distilled water, yield a preparation which is approximately equivalent to distilled aromatic water in strength, but contains about 1.5 p.c. v/v of alcohol (90 p.c.).

Aqua Sterilisata. *Sterilised Water.*—Distil potable water into a previously *sterilised* glass receiver, and transfer the freshly distilled water to a *sterilised* hard glass container. Close the container to exclude bacteria, sterilise by heating in an autoclave, or by boiling for thirty minutes.

Cataplasmata. Poultices are thick pasty preparations intended for local application, either cold or hot. Only one preparation, viz.—

Cataplasma Kaolini. *Kaolin Poultice.*—Kaolin (finely sifted) 527 grms., boric acid (finely sifted) 45 grms., methyl salicylate 2 mils., oil of peppermint 0.5 mil., thymol 0.5 grm., glycerin 425 grms.

N.B.—Should be kept in a well-closed container.

Collodia.—Collodions are solutions of drugs in collodion, or solution of pyroxylin in ether and alcohol.

Collodium Flexile.—Pyroxylin 2 gm., colophony 3 gm., castor oil 2 gm., alcohol (90 p.c.) 24 mils, ether q.s. to 100 mils. The alcohol (90 p.c.) may be replaced by industrial methylated spirit of the same strength.

Confectiones.—Confections, Electuaries or Conserves are soft preparations of drugs, made into a paste with sugar or honey, either to give them a pleasant and agreeable taste, or to preserve them. The dose of all confections is **60 to 120 grs. or 4 to 8 grms.** There are only two in the B.P. –

Confectio	Ingredients	Strength	Action and uses
Sennæ	Powdered senna leaf 10 gms., powdered coriander 4 gms., figs 16 gms., tamarind and cassia pulp, each 12 gms., prunes 8 gms., extract of liquorice 1½ gms., sucrose 40 gms., water q.s. to 100 gms.	10 p.c.	A safe and elegant laxative in chronic constipation.

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Confectio	Ingredients	Strength	Action and uses
Sulphuris	Precipitated sulphur 450 gms., acid pot. tartrate 110 gms., tragacanth 5 gms., syrup 210 mils., tincture of orange 55 mils., glycerin 170 mils.	45 p.c.	A gentle laxative.

Effervescents Granular, or those preparations that effervesce when mixed with water. All are granular. They are prepared by the admixture of acids and alkalies. **Pulvis Effervescens Compositus** (*Seidlitz Powder)* is described under powders.

The following are the B.P. granular effervescing preparations, the quantities of which are given in grammes :—

Effervescent	Composition	Dose	Action and uses
Sodium Phosphate	Sodium phosphate 50, sod. bicarb. 50, tartaric acid 24, citric acid 21	60 to 240 grs. (4 to 16 gms.)	A mild aperient.
Sodium Sulphate	Sod. bicarb. 50, sod. sulph. 50, tartaric acid 24, citric acid 21	60 to 240 grs. (4 to 16 gms.)	Hydragogue purgative

Elixiria. Elixirs are weak tinctures of drugs rendered pleasant and agreeable by admixture of sugar and aromatics. Only one in the B.P., viz.—

Elixir Cascaræ Sagradæ.—Cascara sagrada in coarse powder 1000 gms., liquorice unpeeled, in coarse powder 125 grm., light magnesium oxide 150 grms., soluble saccharin 1 grm., oil of coriander 0.15 mil, oil of anise 0.2 mil., alcohol (90 p.c.) 12.5 mils., glycerin 300 mils., distilled water q.s. to 1000 mils. *Dose.*—2 to 4 mils or 30 to 60 ms.

Emplastra. Plasters.—Four in number. They are made of adhesive substances spread upon cloth or leather so as to adhere to the skin. They are applied for the purpose of holding medicinal substances in contact with the body, of acting as a protective and support, or of bringing the edges of a wound together.

Emplastrum	Materials used	Strength	Action and uses
Belladonnæ	Powdered root percolated with alcohol and water to make an extract. Mix with colophony plaster to required strength.	0.25 p.c. of alkaloids	A local anodyne. In lumbago, neuralgia, swollen and painful glands
Cantharidini	Cantharidin 2 gm., acetone 100 ml., castor oil 200 gm., yellow bees-wax 400 gm., wool fat 398 gm.	0.2 p.c. of cantharidin	Vesicant
Colophonii	Colophony 10 gm., lead plaster 85 gm., hard soap 5 gm.	1 in 10	For strapping wound.
Plumbi	Lead monoxide 4 gms., olive oil 8 gms., water 4 mls. or q.s.	.....	Sedative and protective

Extracta. Extracts.—These are prepared by extracting the active principles either with water, alcohol, or both, or with ether. They contain different active principles in a very concentrated form with very little inert substance. Different methods are used for extraction, viz., *maceration*, *infusion*, *percolation* and *decoction.* According to the consistency of the different extracts they have been divided into, **Dry or Solid, Semisolid or Soft,** and **Liquid.**

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The B.P. directs that the industrial methylated spirit of equivalent strength may be substituted in place of alcohol in the preparation of the different extracts provided no industrial methylated spirit is left in the finished product.

Of the different extracts, Ext. Fellis Bovini, Ext. Hepatis Liq., Ext. Hepatis Sic., and Ext. Pituitarii Liq., are animal products.

Semisolid or Soft Extracts are prepared by dissolving, macerating, infusing or boiling drugs in cold and hot distilled water, and evaporating the solution, infusion or decoction, as the case may be, to the consistence of a soft extract. They are six in number.

Extractum	Source	Process	Menstruum	Dose
Cinchonæ	Cinchona 1000 gm., glycerin, and alcohol q. s. (4/5 gr. alkaloids in 8 grs.)	P. & E.	Alcohol	2 to 8 gr. (0.12 to 0.5G.)
Fellis Bovini	Ox gall	E.	Alcohol	5 to 15 gr. (0.3 to 1 G.)
Gentianæ	Sliced root dried	M.D. & E.	Water	2 to 8 grs. (0.12 to 0.5 G.)
Glycyrrhizæ	Dried root	M.D. & E.	Chloroform water	10 to 30 grs. (0.6 to 2 G.)
Malti	Malted grain of barley	D. E.	Water	60 to 240 ms. (4 to 16 ml.)
Malti c. Oleo Morrhuæ	Malt extract 9 G., Cod-liver oil 1 G. (15% Cod-liver oil.)		....	60 to 240 ms. (4 to 16 ml.)

Except Extractum Cinchonæ which has been diluted with glycerin to contain $\frac{4}{5}$ gr. of total alkaloids in 8 grs., the strengths of the soft extracts are not adjusted, but since they do not contain any potent principle this is of little consequence.

Liquid Extracts are prepared from drugs, with water as the solvent and about 20 p.c. alcohol is added for their preservation against fermentation and fungoid growth. Ext. Cinchonæ Liq. is prepared from soft extract. They are fourteen in number:

Extractum	Ingredients	Alcohol p c. in the menstruum	Strength	Dose
Belladonnæ Liq.	Belladonna root, alcohol, water	90	0.75 p.c. alkaloids	1/4 to 1 m. 0.015-0.06 ml.
Cascaræ Sag. Liq.	Cascara powder 1000 G., alcohol 250 ml., water q.s. to 1000.	90	1 in 1	30 to 60 ms. 2 to 4 mls.
Cinchonæ Liq.	Ext. cinchon. 50 G., hydrochloric acid 3 ml., glycerin 10 ml., alcohol 25 ml., water q. s. to 100 ml.	90	5 p.c. alkaloids	5 to 15 ms. 0.3 to 1 ml.
Colchici Liq.	Colchicum seed 1000 G., alcohol q.s. 1000 ml.	60	0.3 p.c. colchicine	2 to 5 ms. 0.12 to 0.3 ml.
Ergotæ Liq.	Ergot 1000 G., tartaric acid, alcohol each q.s	50	0.06 to 0.04 p.c. ergotoxine	10 to 20 ms. 0.6 to 1.2 ml
Glycyrrhizæ Liq.	Liquorice 1000 G, chloroform water and alcohol q.s.	90	Sp. gr. 1.200	30 to 60 ms 2 to 4 mls.

D=Decoction. E=Evaporation. I=Infusion. P=Percolation. M=Maceration.

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Extractum	Ingredients	Alcohol p.c. in the menstruum	Strength	Dose
Hamamelidis Liq.	Hamamelis 1000 G., alcohol q.s. to 1000 ml.	45	1 in 1	30 to 60 ms. 2 to 4 ml.
Hepatis Liq.	Liver of ox or sheep, glycerin, alcohol, water.	95	1 oz. equal to 8 oz. fresh liver.	1 oz. or 30 mils
Hyoscyami Liq.	Hyoscyamus powder 1000 G., alcohol q.s.	70	0.05% of alkaloids	3 to 6 ms. 0.2 to 0.4 ml.
Ipecacuanhæ Liq.	Ipecac. powder 1000 G., alcohol q.s.	90	2 p.c. emetine	½ to 2 ms. or 10 to 30 ms.
Nucis Vomicæ Liq.	Nux vomica 1000 G., alcohol q.s.	45 & 70	1.5 p.c. strychnine	1 to 3 ms. 0.06 to 0.2 ml.
Pituitarii Liq.	Posterior lobe of pituitary of ox, water and acetic acid.	....	10 Unit per mil.	2 to 5 Units 0.2 to 0.5 ml. (subcutaneously)
Senegæ Liq.	Senega 1000 G., dilute solution of ammonia q.s., alcohol q.s. to 1000 ml.	60	1 in 1	5 to 15 ms. 0.3 to 1 ml.
Sennæ Liq.	Senna fruit 1000, alcohol 250 ml., chloroform water q.s. 1000 ml.	90	1 in 1	10 to 30 ms. 0.6 to 2 mls.

N. B.—Extract of male fern, extract of malt and malt with cod liver oil are thick viscid liquids, though they are not called liquid extracts in the B.P.

From the above table it will be gathered that all the liquid extracts except pituitary, require alcohol of various strengths, either for their preparation or for their preservation. Extract of Male Fern being prepared with ether is given in the table of **Ethereal Extracts.**

In the preparation of liquid extract of colchicum, the seeds are first treated with light petroleum to remove fat before adding alcohol; while the liquid extract of ergot is treated with light petroleum to remove fat and then prepared with alcohol acidified with tartaric acid: and pituitary extract with alcohol acidified with acetic acid.

The *strength* of liquid extracts not containing any potent principle is so adjusted that one part by weight of the drug produces one part by volume of the finished product, *i.e.*, the strength is 1 in 1. In the case of extracts of powerful drugs, the strength is adjusted to a definite percentage of the active principle based on the average percentage of the active principle present in the crude drug. Thus the liquid extract of ipecacuanha is so adjusted that it should contain 2 p.c. *emetine*, *i.e.*, the alkaloid strength contained in ipecacuanha.

Ethereal Extracts are prepared by percolating dry drugs with ether. There is only one in the B.P.:—

Extractum	Ingredient	Process	Menstruum	Strength	Doses
Filicis	Male Fern	P.	Ether	25 p.c. Filicin.	45 to 90 ms. (3 to 6 mils)

Dry Extracts, sometimes called **abstracts,** are alcoholic or watery extracts mixed with an inert powdered substance and then dried and powdered. They are nine in number.

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Extractum	Ingredients	Process	Strength	Dose
Belladonnæ Sic.	Belladonna leaves, alcohol 70 p.c.	P. & E.	1 p.c. Alkaloids	1/4 to 1 gr. 0.015-0.06 G.
Cascaræ Sagradæ Sic.	Powdered cascara sagrada and water.	P. & E.	.....	2 to 8 grs. 0.12 to 0.5 G
Colchici Sic.	Colchicum corm 1000 G., alcohol (60 p.c.) and lactose each q.s.	P. & E.	1 p.c. colchicine	1/4 to 1 gr. 0.015-0.06 G.
Colocynth Co.	Colocynth 27 G., aloes 56 G., scammony 18 1/2 G., curd soap powder 14 G., cardamom 4 1/2 G., alcohol (60 p.c.) 700 ml.	M. & E.	27 p.c.	2 to 8 gr. 0.12 to 0.5 G.
Hepatis Sic.	Trimmed ox or sheep liver, alcohol (80 p.c.), sulphuric acid and water.	E.	....	Equivalent to 1/2 lb. of fresh liver.
Hyoscyami Sic.	Hyoscyamus 1000 G., alcohol (70 p.c.) q.s.	P. & E.	0.3 p.c. alkaloid	1/4 to 1 gr. 0.016-0.06 G.
Krameriæ Sic.	Krameria, water.	P. E.	.....	5 to 15 grs. 0.3 to 1 G.
Nucis Vomicæ Sic.	Nux vomica 1000 G., alcohol (70 p.c.), cal. phosphate each q.s.	P. E.	5 p.c. strychnine	1/4 to 1 gr. 0.015-0.06 G.
Opii Sic.	Opium, water, calcium phosph.	E.	1/2 gr. morphine in 1 gr	1/4 to 1 gr. 0.015-0.06 G.

The following extracts are standardised :—

Ext. Belladonnæ Liq.
„ „ Sic.
„ Cinchonæ
„ „ Liq.
„ Colchici Liq.
„ „ Sic.
„ Ergot. Liq.
„ Hyoscyam. Liq.
„ „ Sic.
Ext. Ipecac. Liq.
„ Nucis Vom. Liq.
„ „ Sic.
„ Opii Sic.
„ Pituitarii Liq.

Because of the variations in the strengths of the different preparations, there is very little uniformity in the dosage of the different extracts. The student should however try to remember the maximum doses of the extracts containing powerful active principles.

Names of extracts	Maximum dose
Belladonnæ Liquid.	1 minim
Ipecac. Liq.	2 ms.
Nucis Vomicæ Liq.	3 ms.
Colchici Liq.	5 ms.
Hyoscyami Liq.	6 ms.
Ergot. Liq.	20 ms.
Bellad. sic., Colchici sic., Hyoscyam. sic., Nucis Vom. sic., Opii sic.	1 gr.

Gelatinum. Gelatin pastes are mixtures of gelatin, glycerin and water in varying proportions, and are non-irritating protectives to the skin. They should be melted before use and applied with a brush. There is only one preparation.

Gelatinum Zinci. *Syn.—Unna's Paste.*—Zinc oxide, gelatin cut small, each 150 grm., glycerin 350 grm., distilled water 350 mils or q.s.

Glycerina.—Glycerins are solutions of drugs in plain glycerin or glycerin and water. Because of the high viscosity of glycerin these preparations adhere to the mucous surface over which they are applied, therefore they are very popular as throat applications where

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the demulcent action of glycerin also comes into play. Phenol having greater affinity for glycerin than water, Glycerinum Phenolis does not act as a caustic. They are six in number:—

Glycerinum	Ingredients	Dose	Action
Acidi Borici	Boric acid 31 G., glycerin q.s. to 100 G.	10 to 30 ms.	Antiseptic.
Acidi Tannici	Tannic acid 15 G., glycerin 85 G.	10 to 30 ms.	Astringent.
Aluminis	Alum 13 G., water 6 mls., glycerin 81 G.	30 to 60 ms.	Do.
Amyli	Starch 85 G., water 170 mls., glycerin 745 G.	.....	Emollient.
Boracis	Borax 12 G., glycerin 88 G.	30 to 60 ms.	Antiseptic, emollient.
Phenolis	Phenol 16 G., glycerin 84 G.	5 to 15 ms.	Antiseptic.

Infusa Recens.—Fresh Infusions are watery solutions of vegetable principles, prepared by soaking in cold or boiling water, coarsely powdered or bruised crude drugs for a certain time in a covered vessel, and then straining the liquid. **Quassia and calumba** only are infused in **cold water**. The amount of water in all cases is 1000 mils. All infusions become inky with persalts of iron, except those of quassia and calumba. They should always be prepared fresh, and the prescriber should always specify "recens" when fresh infusion is required. To a student, the infusion of **digitalis** is most important. It contains **0.05 Unit** of activity in **1 mil**, and one-twentieth of the strength of the tincture. The **dose is 6 to 20 mils or 90 to 300 ms. For a single dose it is given in 30 to 120 mils or 1 to 4 oz.** They are nine in number.

For dispensing purposes, fresh infusion should be used within twelve hours of its preparation.

Infusum	Ingredients	Strength	Time in minutes	Dose
Aurantii Rec.	Dried bitter-orange peel cut small 50 G., boiling water 1000 G.	1 in 20	15	½ to 1 oz.
Buchu Rec.	Buchu leaves broken 50 G., boiling water 1000 G.	1 in 20	15	1 to 2 oz.
Calumbæ Rec.	Calumba 50 G., cold water 1000 mil.	1 in 20	30	½ to 1 oz.
Caryophylli Rec.	Clove bruised 25, boiling water 1000 G.	1 in 40	15	½ to 1 oz.
Digitalis Rec.	Digitalis leaves powdered 5 gms., and boiling water 1000 G.	0.05 Unit in 1 mil	15	90 to 300 ms. or 1 to 4 oz.
Gentianæ Co. Rec.	Gentian root thinly sliced 12.5 gms., dried bitter orange peel cut small 12.5 gms., lemon peel small 25 gms. boiling water 1000 gms.	1 to 80	15	½ to 1 oz.
Quassiæ Rec.	Quassia rasped 10 G., cold water 1000 mils.	1 in 100	15	½ to 1 oz.
Senegæ Rec.	Senega powdered 50 G., boiling water 1000 G.	1 in 20	30	½ to 1 oz.
Sennæ Rec.	Senna fruit 100 gms., ginger sliced 5 gms., boiling water 1000 grms.	1 in 10	15	½ to 2 oz.

Infusa Concentrata. Concentrated infusions are solutions of drugs in alcohol, prepared either by percolation or maceration, to be diluted

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with seven times their volume of distilled water, when they become approximately equivalent in strength, but not in flavour, to fresh infusions, but containing only a small proportion of alcohol. They are eight in number.

N. B.—Infusions of senna, both fresh and concentrated, are now prepared with fruits and not with leaves as before.

Infusum	Ingredients	Process	Dose
Aurantii Conc.	Dried bitter orange peel 400 grm., alcohol (25 p.c.) 1350 mils.	M.	2 to 4 mils. 30 to 60 ms.
Buchu Conc.	Buchu freshly broken 400 grms., alcohol (25 p.c.) q.s. 1000 mils.	P.	4 to 8 mils. 60 to 120 ms.
Calumbæ Conc.	Calumba cut small 400 grm., alcohol (90 p.c.) 250 mils., distilled water q.s. to 1000 mils.	M.	2 to 4 mils. 30 to 60 ms.
Caryophylli Conc.	Clove bruised 200 grm., alcohol (25 p.c.) 1100 mils.	M.	2 to 4 mils. 30 to 60 ms.
Gentianæ Compositum Conc.	Gentian sliced 100 grm., dried bitter orange peel 100 grm., lemon peel 200 grm., alcohol (25 p. c.) 1200 mils.	M.	2 to 4 mils. 30 to 60 ms.
Quassiæ Conc.	Quassia rasped 80 grm., alcohol (90 p.c.) 250 mils., distilled water q.s. to 1000 mils.	M.	2 to 4 mils. 30 to 60 ms.
Senegæ Conc.	Senega 400 grms., dilute solution of ammonia and alcohol (25 p.c.) each q.s. to 1000 mils.	P.	2 to 4 mils. 30 to 60 ms.
Sennæ Conc.	Senna fruit 800 grm., Strong tr. of ginger 80 mil., alcohol (20 p.c.) q.s. to 1000 mils.	P.	2 to 4 mils. 30 to 60 ms.

Injectio. Injections are solutions or suspensions of drugs intended for injection into the muscle, except Injectio Sodii Chloridæ et Acaciæ which is meant for intravenous injection. They are six in number.

Injectio	Ingredients	Strength	Dose
Bismuthi	Precipitated bismuth 20 grm., dextrose 5 grm., cresol 0.5 mil., fresh distilled water q.s. 100 mils.	3 grs. in 15 ms.	0.5 to 1 ml. 8 to 15 ms.
Bismuthi Salicylatis	Bismuth salicylate 10 grm., camphor, phenol each 1 grm., olive oil q.s. to 100 mils.	2 grs. in 20 ms.	0.6 to 1.2 mls. 10 to 20 ms.
Ferri	Solution of ferric chlor. 7 mils., citric acid 2 grm., dilute solution of ammonia and distilled water q.s., sterile water q.s. to 100 mils.	½ gr. iron and ammon. cit. in 30 ms.	1 to 2 mils. 15 to 30 ms.
Hydrargyri	Mercury 10 grm., wool fat 50 grm., camphor 10 grm., creosote 10 mils., olive oil 23 mil.	1 gr. Hg. in 10 ms.	0.3 to 0.6 mil. 5 to 10 ms.
Hydrargyri Subchloridi	Calomel 5 grm., wool fat 50 grm., camphor 10 grm., creosote 10 mil., olive oil 23 mil.	1 gr. calomel in 20 ms.	0.6 to 1.2 mil. 10 to 20 ms.
Sodii Chloridi et Acaciæ	Sodium chloride 9 grm., acacia 60 grm., fresh distilled water q.s. to 1000 mils.	0.9 p.c.	

Lamellæ.—**Eye-discs** are thin plates or discs of medicated gelatin with glycerin, used in ophthalmic practice. These are prepared by dissolving gelatin 18 gms., in glycerin 2 gms., and water 88 gms. or *q.s.* They are four in number:—

Note.—M = Maceration. P = Percolation.

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Lamella	Composition	Strength in each	Action
Atropinæ	Discs of gelatin with glycerin weighing about 1/50 gr. each.	1/5000 gr.	Mydriatic
Cocainæ	Discs of gelatin with glycerin weighing about 1/20 gr. each.	1/50 gr.	A local anæsthetic
Homatropinæ	Discs of gelatin with glycerin weighing about 1/22 gr. each.	1/100 gr.	Mydriatic
Physostigminæ	Discs of gelatin with glycerin weighing about 1/50 gr. each.	1/1000 gr.	Myotic

Linimenta.—Liniments or Embrocations are preparations used for rubbing or painting over the skin. The majority of them are limpid liquids. Camphor enters into their composition for its local stimulant action, and also to lessen the risk of these being taken internally as it has a characteristic strong smell. It must be remembered that Linimentum Terebinthinæ Aceticum should not be mixed with Linimentum Ammoniæ, as by this admixture a chemical combination takes place which neutralises the effects of both the ammonia and acetic acid. They are seven in number.

Linimentum	Preparation	Strength	Action and uses
Aconiti	Aconite 50 G., camphor 3 G., alcohol (90 p.c.) q.s. 100 mls.	50 p.c.	A powerful local sedative and anodyne.
Belladonnæ	Belladonna root 1000 G., camphor, alcohol (90 p.c.), water, each q.s. to produce the required strength.	0.375 p.c. alkaloids	A powerful local anodyne. In neuralgia, etc.
Camphoræ	Camphor in flowers 2 G., and olive oil 8 G.	1 in 5	A local stimulant
Camphoræ Ammoniatum	Camphor 125 gms., oil of lavender 5 mils., strong solution of ammonia 250 mils., and alcohol (90 p.c.) to 1000 mils.	1 in 8	Rubefacient and counter-irritant
Saponis	Soft soap 80 gms., camphor 40 gms., oil of rosemary 15 mils., alcohol (90 p.c.) q.s. to 1000 mils., and water 170 mils.	1 in 12½	A stimulant application to sprains and bruises
Terebinthinæ	Soft soap 75 gms., camphor 50 gms., oil of turpentine 650 mils., water q.s. to 1000 mils.	65 p.c.	Irritant and rubefacient
Terebinthinæ Aceticum	Glacial acetic acid 110 mils., liniment of camphor 445 mils., oil of turpentine q.s. to 1000 mils.	1 in 9	Powerful rubefacient

Liquores.—Solutions are solutions of vegetable, animal or inorganic substances in distilled water, either alone or with other solvents. Liqr. Adrenalini Hydrochlor. and Liqr. Epispasticus are obtained from the animal kingdom. Liqr. Epispasticus is prepared with acetone. Most of the vegetable solutions are made with the aid of alcohols of various strengths. They are twenty-nine in number:—

Liquor	Composition	Strength	Dose
Adrenalini Hydroch.	Adrenaline 1 G., chlorbutol 5 G., sodium chloride 9 G., acid. hydrochlor. dil. 3 ml., water q.s. to 1000 mls.	1 in 1000 or 0.1 p.c.	2 to 8 ms. subcutaneously
Ammoniæ Dil.	Strong solution of ammonia 333 mls., water q.s. 1000 ml.	10 p.c. w/w	10 to 20 ms. 0.6 to 1.2 ml.
Ammoniæ Fortis	.....	32.5 p.c. by weight	Used externally
Ammonii Acetatis Dil.	Strong solution of ammon. acet. 125 ml.; water q.s. to 1000 ml.	7.2 p.c.	¼ to 1 oz. 8 to 30 ml.

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Liquor	Composition	Strength	Dose
Ammonii Acetatis Fortis	Acid acetic glacial 453 G., ammon. carb. 330 G., liq. ammon. fort. 100 ml. or q.s., water q.s. to 1000 ml.	57.5 p.c.	15 to 60 ms. 1 to 4 ml.
Arsenicalis	Arsenic trioxide 10 G., liq. pot. hydrox. 100 ml., acid hydrochlor. dil. 28 ml., or q.s., water q.s. to 1000 mls.	1 p.c.	2 to 8 ms. 0.12 to 0.5 ml.
Arseni et Hydrargyri Iodidi	Arsenic triiodide 1 G., red mercuric iodide 1 G., water q.s. to 100 ml.	1 p.c. of each	5 to 15 ms. 0.3 to 1 ml.
Calcii Hydroxidi	Calcium hydroxide 1 G., water 100 ml.	0.15 p.c.	1 to 4 oz. 30 to 120 ml.
Cresolis Saponatus	Cresol 500 ml., linseed oil 180 G., Pot. hydroxide 42 G., water q.s. to 1000 mils.	50 p.c.	Used externally
Epispasticus	Cantharidin 4 gms., castor oil 25 mils., colophony 12 grms., acetone q.s. to 1000 mils.	0.4 p.c.	Used externally
Ergosterolis Irradiati	Ergosterol irradiated by ultra violet ray	1 G. contains 3000 unit antirachitic vitamin	5 to 15 ms. or 25 to 50 ms.
Ferri Perchloridi	An aqueous solution of $FeCl_2$. Obtained by oxidation of ferrous chloride.	15 p.c. ferric chlor.	5 to 15 ms. 0.3 to 1 ml.
Formaldehydi	An aqueous solution	37 to 41 p.c.	.....
Glycerylis Trinitratis	Solution of glyceryl trinitrate in alcohol	1/60 gr. in 2 ms.	1/2 to 2 ms. 0.03-0.12 ml.
Hydrargyri Perchloridi	Mercuric chloride 1 gm., and water q.s. 1000 mils.; by solution	1/16 gr. in 60 ms.	30 to 60 ms. 2 to 4 mils.
Hydrogenii Peroxidi	An aqueous solution of hydrogen peroxide	10 of oxygen in 1	30 to 120 ms. 2 to 8 mils.
Iodi Fortis (Tr. Iodi Fort.)	Iodine 10 G., pot. iodide 6 G., water 10 ml., alcohol (90 p.c.) q.s. to 100 ml.	10 p.c. iodine 6 p.c. pot. iodide	Used externally
Iodi Mitis (Tr. Iodi Mitis)	Iodine 2 1/2 G., pot. iodide 1 1/2 G., water 2 1/2 ml., alcohol (90 p.c.) q.s. 100 ml.	2.5 p.c. iodine 1.5 p.c. pot. iodide	5 to 30 ms 0.3 to 2 ml.
Iodi Simplex	Iodine 9 G., alcohol (95 p.c.) q.s. to 100 ml.	1 1/2 gr. in 15 ms.	3 to 15 ms. 0.2 to 1 ml
Magnesii Bicarbonatis	A solution of magnes. bicarbonate in water saturated with CO_2.	2.5 p.c.	1 to 2 ozs. (30 to 60 mils.)
Morphinæ Hydrochloridi	Morphine hydrochloride 1 gm., diluted hydrochloric acid 2 mils., alcohol (90 p.c.) 25 mils., and water q.s. to 100 mils.	1/4 gr. in 30 ms. or 1 p.c.	5 to 30 ms. 0.3 to 2 ml.
Picis Carbonis	Prepared coal tar 2 gms., quillaia bark in powder 1 gm., and alcohol (90 p.c.) q.s. to 10 mils.	1 in 5	Used externally
Plumbi Subacetatis Dil.	Strong lead subacetate solution 12.5 mils., water q.s. to 1000 mils.	1.25 p.c. liquor	Used externally
Plumbi Subacetatis Fortis	Lead acetate 250 gms., lead monoxide in powder 175 gms., and water q.s. to 1000 mils.	19 to 21.5 p.c. lead	Used externally
Potassii Hydroxidi	An aqueous solution containing 5 p.c. of total alkali. (KOH).		Used externally
Quininæ Ammoniatus	Quinine sulph 2 G., dilute sol. ammon. 10 ml., alcohol (60 p.c.) q.s. to 100 ml.	1 1/3 gr. in 60 ms.	30 to 60 ms. 2 to 4 ml.
Sodæ Chlorinatæ Chirurgicalis	Chlorinated lime, boric acid, sod. carb. each q.s., water 1000 ml.	0.5 to 0.55 p.c. chlorine	Used externally
Sodii Chloridi Physiologicus	Sodium chloride 9 G., water q.s. 1000 ml.	0.9 p.c.	.....
Strychninæ Hydrochloridi	Strychnine hydrochloride 1 gm., alcohol (90 p.c.) 25 mils., and water q.s. to 100 mils.	1 p.c. or 1/9 gr. in 12 ms.	3 to 12 ms. 0.2 to 0.8 ml.

The following liquors are all 1 p.c., *i.e.* contain 1 gr. in 110 ms. :— Liquor arsenicalis, arseni et hydrarg. iodidi, glycerylis trinitratis, morphinæ hydrochlor., strychninæ hydrochlor.

The following liquors are meant for external use only :— Liquor ammoniæ fort., Liq. cresolis saponatus, Liq. epispasticus,

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Liq. formaldehydi, Liq. picis carbonis, Liq. plumbi subacetatis fort. and dilutus, Liq. potassii hydroxidi, Liq. sodæ chlorinatæ chirurgicalis.

Lotiones.—**Lotions** are solutions or mixtures of active ingredients for external application only. There is only one.

Lotio	Composition	Strength	Action and uses
Hydrargyri Nigra	Mercurous chloride 7 gms., glycerin 50 mils., solution of cal. hydroxide q.s. to 1000 mils.	0.7 p.c.	A stimulating alterative application to syphilitic sores

Mella.—**Mellita. Honeys** are liquid preparations containing mostly honey as a vehicle. They are three in number :—

Mel Depuratum is honey melted and strained through flannel.

Mel	Preparation	Strength	Dose	Action
Boracis	Borax 10 gms., purified honey 85 gms. and glycerin 5 gms.	1 in 10	Used locally	An alterative to diseased mucous surface
Oxymel	Acetic Acid 15, water 15, honey q.s. to 100 ml.	sp. gr. 1.258 to 1.263	30 to 120 ms. (2 to 8 mils.)	Expectorant. Used as a vehicle
Oxymel Scillæ	Squill 5 G., acetic acid 9 ml., water 25 ml., honey q.s.	5 p.c. squill	30 to 60 ms. (2 to 4 mils.)	Expectorant.

Misturæ.—**Mixtures** are preparations in which drugs are simply dissolved in water or suspended in it. The official mixtures are only two in number.

Mistura	Preparation	Strength	Dose
Magnesii Hydroxidi (Cream of Magnesia)	Mag. sulph. 47.5 G., sodium hydroxide 15 G., light mag. oxide 52.5 G., water q.s. 1000 ml.	12½ gr. in 240 ms.	60 to 240 ms. 4 to 16 ml.
Sennæ Composita	Magnesium sulphate 25 gms., liquid extract of liquorice 5 mils., tinct. card. co. 10 mils., spt. ammon. aromat. 5 mils., and fresh infusion of senna q.s. to 100 mils.	2 dr. in 1 oz or 25 p.c. mag. sulph	1 to 2 ozs. 30 to 60 mils.

Mucilagines.—**Mucilages** are solutions of gummy substances in water. They are two in number, viz. :—

Mucilago	Ingredients	Dose
Acaciæ	Acacia 40 G., chloroform water 60 ml.	60 to 240 ms. 4 to 16 mls.
Tragacanthæ	Tragacanth 12.5 G., alcohol (90 p. c.) 25 ml., chloroform water q.s. to 1000 mls.	60 to 240 ms. 4 to 16 mls.

Oculenta. Eye ointments are preparations meant for application to the eye. They are prepared as follows :—

Melt together 90 parts by weight of yellow soft paraffin and 10 parts by weight of wool fat, filter while hot and sterilise by heat at 150° for one hour. The drug required for 100 grms. is mixed in a sterile mortar and the melted basis added to weigh 100 grms.

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Oculentum	Ingredients	Strength
Atropinæ	Atropine sulph.	0.25 p.c.
Atropinæ c. Hydrargyri Oxido	Atropine sulphate, yellow mercuric oxide	0.125 p.c. 1 p.c.
Cocainæ	Cocaine hydrochloride	0.25 p.c.
Hydrargyri Oxidi	Yellow mercuric oxide	1 p.c.
Hyoscinæ	Hyoscine hydrobromide	0 125 p.c.
Iodoformi	Iodoform	4 p.c.
Physostigminæ	Physostigmine salicylate	0.125 p.c.

Oleata.—**Oleates** are preparations of bases with oleic acid, having a solid or semi-solid consistence. Only one preparation is in the B.P., viz :—

Hydrargyrum Oleatum.—Yellow mercuric oxide 20 gms., liquid paraffin 5 gms., oleic acid 75 gms.

Olea. Oils.—There are thirty oils in the B.P. They can be grouped under two classes—fixed and volatile; the former being obtained by expression, and the latter by distillation, except in the case of lemon oil which is a volatile oil though obtained by expression. Oil of cade is obtained by dry or destructive distillation.

Of the ten fixed oils, cod-liver oil is an animal product, and the rest are expressed at ordinary temperatures. Oil of theobroma is solid in cold weather and semi-solid or fluid in hot weather. The colour of cajuput is deep-green and that of cade is almost black. Oil of turpentine is almost colourless. The rest display various shades of straw, yellow and pale-brown.

Fixed or Expressed Oils

Oleum	Source	Dose	Action
Amygdalæ	Bitter or sweet almonds	½ to 1 oz.	Demulcent, emollient
Arachis	Seeds	½ to 1 oz.	Emollient
Gossypii Seminis	Seeds	½ to 1 oz.	Emollient and demulcent
Hydnocarpi	Seeds. By cold expression	5 to 15 ms. up to 60 ms.	In leprosy
Lini	Linseed	½ to 1 oz.	Demulcent and emollient
Morrhuæ	Expressed from the fresh liver of Cod	30 to 120 ms.	Nutritive, tonic and alterative
Olivæ	Ripe fruit	½ to 1 oz.	Emollient
Ricini	Fresh seeds	60 to 240 ms.	Cathartic
Sesami	Seeds	½ to 1 oz.	Emollient
Theobromatis	Expressed from roasted seeds	Used externally	For making suppositories

Volatile, Essential or Distilled Oils

Oleum	Source	Dose	Action
Abietis	Fresh leaves	....	Rubefacient
Anethi	Dill fruit	1 to 3 ms.	Carminative
Anisi	Anise or star-anise	1 to 3 ms.	Do
Cadinum	Woody portions; by destructive distillation	Used externally	A stimulating application
Cajuputi	Fresh Leaves	1 to 3 ms.	Antispasmodic
Cari	Caraway fruit	1 to 3 ms.	Carminative, antispasmodic
Caryophylli	Cloves	1 to 3 ms.	Do
Chenopodii	Fresh plants	3 to 15 ms.	Anthelmintic

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Oleum	Source	Dose	Action
Cinnamomi	Cinnamon	1 to 3 ms.	Antispasmodic
Coriandri	Coriander fruit	1 to 3 ms.	Do.
Eucalypti	Fresh leaves	1 to 3 ms.	Antiseptic
Hydnocarpi Aethylicum	Esterifying fatty acids of hydnocarpus oil with ethyl alcohol and subsequent distillation	5 to 15 ms. increasing to 60 ms.	In leprosy
Lavandulæ	Fresh flowering tops	1 to 3 ms.	Antispasmodic
Limonis	Fresh lemon peel by expression	1 to 3 ms.	Aromatic
Menthæ Piperitæ	Fresh flowering tops	1 to 3 ms.	Antispasmodic and carminative
Myristicæ	Nutmeg	1 to 3 ms.	Carminative and narcotic
Rosmarini	Flowering plant	1 to 3 ms.	Rubefacient
Santali	Wood of Santalum album	5 to 15 ms.	Urinary antiseptic
Santali Australiensis	Wood of *Eucarya spicata*	5 to 15 ms.	Do.
Terebinthinæ	From oleo-resin, turpentine	3 to 10 ms. or 120 to 240 ms. As anthelmintic	Rubefacient, diuretic, and anthelmintic

The dose of most of the volatile oils is from **1 to 3 minims** or **0.06 to 0.2 mil**, with the exception of sandal-wood, **5 to 15 ms.**; chenopodium, **3 to 15 ms.**; and turpentine, **3 to 10 ms.**

Volatile oils are combined with many B.P. pills, either for their carminative effect or because of their smell to serve as a means of distinction between various pill masses of similar appearance.

Pasta. Pastes are prepared like ointments and intended for external application. They are usually spread on lint and covered with a layer of cotton wool and kept in position by bandage, or adhesive plaster.

Pasta Zinci Oxidi Co.—Zinc oxide, starch, each 250 grms., white soft paraffin 500 grms.

Pilulæ.—Pills are solid or semi-solid globular masses containing medicinal agents intended to be swallowed whole without chewing. Pills are always popular for easy administration, being portable, easily swallowed and containing a definite and correct dose. They should not be too hard unless intended to dissolve slowly, or so soft as to lose shape and stick together. To prevent this and to cover the nauseous taste they are coated or gilded. In India and tropical countries, pills get too hard or too soft according to the variations of the weather; being liable to become soft and to run together during the rains. To avoid this, they should be kept in well stoppered bottles. Pills, as a rule, should not weigh more than 5 grains each. A mass of the consistence of firm clay is first made by pounding and kneading the drugs together in a mortar; and subsequently this mass is either rolled and divided by a pill-making machine, or when the quantity is small, the same process is done over a pill-tile by the spatula. The pills should be perfectly round and firm. An excipient is always necessary to make a pill-mass.

The B.P. pills are seven in number. They are:—

Pilula	Composition	Strength	Action
Aloes	Aloes 58 gms., hard soap 29 gms., oil of caraway 3 mils., syr. of glucose 10 gms. or q.s.	58 p.c.	Cathartic
Aloes et Asafœtidæ	Aloes, asafetida, hard soap each 3 gms., syr. of glucose 1 gm. or q.s.	30 p.c.	Cathartic and antispasmodic

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Pilula	Composition	Strength	Action
Aloes et Ferri	Exsiccated ferrous sulph. 10 G., aloes 20 G., cinnamon, cardamom, ginger, each 12 G., syrup of glucose 34 gm. or q.s.	1/5 gr. ferrous sulph. or 1/4 gr. iron in 8 gr.	Cathartic and emmenagogue
Colocynthidis et Hyoscyami	Colocynth 12.5 G., aloes 25 G., scammony resin 25 G., oil of clove 4 ml., curd soap 7 G., ext. Hyosc. sic. 12.5 G., syrup of glucose 14 G., or q.s.	12.5 p.c.	Cathartic
Ferri Carbonatis	Exsiccated ferrous sulphate 34 gms., exsiccated sodium carbonate 21.6 gms., gum acacia 8.4 gms., tragacanth 2 gms., liquid glucose 32 gms., and water 2 mils.	20 p c. (Ferrous Carb.)	Tonic and emmenagogue
Hydrargyri	Mercury 33 G., syrup 14 G., liquid glucose 15 G., glycerin 5 G., liquorice 33 G.	33 p.c.	Alterative and laxative
Rhei Co.	Rhubarb 25, powder aloes 20, myrrh 14, hard soap 14, oil of peppermint 2, syrup of glucose 25, or q.s.	25 p.c.	Stomachic, tonic, and a gentle cathartic

All the cathartic pills in the above table contain aloes except the mercurial pill. All pills are given in **4 to 8 grain** doses, except Pil. Ferri Carbonatis, **5 to 30 grs.**

The colour of the B.P. pill-masses is blackish-brown or black, with the exception of Pil. Hydrargyri, which is blue. Many of the pills can be recognised by their smell, for instance, Pil. Rhei Co. by the smell of peppermint; and Pil. Aloes et Asafœtidæ by that of asafetida.

Pulverata. Powders of crude drugs intended for internal use. They are reduced to a fine powder, assayed and adjusted to contain a definite percentage of active ingredients by addition of lactose, the object being to maintain a uniform percentage of active principles. They are six in number.

Pulverata	Ingredients	Strength	Dose
Belladonna	Leaf. Contains 0.3 p.c. hyoscyamine	1/100 gr. alkaloids in 3 grs.	1/2 to 3 grs. 0.03 to 0.2 gm.
Digitalis	Leaf reduced to No. 20 powder, adjusted to contain 10 Units in 1 G.	6 Units in 10 grs.	1/2 to 1 1/2 grs. or 3 to 10 grs. single dose
Ipecacuanha	Ipecacuanha reduced to a fine powder; contains 2 p.c. of emetine	1/25 gr. in 2 grs.	1/2 to 2 grs. or 15 to 30 grs. single dose
Jalapa	Jalap reduced to fine powder	10 p.c. resin	5 to 20 grs. 0.3 to 1.2 gms.
Nux Vomica	Nux vomica. 1.2 p.c. strychnine	1/20 gr. in 4 grs.	1 to 4 grs.
Opium	Opium. Adjusted to contain 10 p.c. morphine	3/10 gr. in 3 grs.	1/2 to 3 grs.

Pulveres.—Powders are mixtures of dry substances reduced to a fine powder and intimately mixed together. Powders should be mixed in a very clean mortar (a glass one being the best). The method of mixing greatly affects the miscibility of powders.

The B.P. powders are eight in number, and they are as under:—

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Pulvis	Composition	Strength	Dose	Action
Cretæ Aromaticus	Cinnamon 10, nutmeg 8, clove 4, cardamom 3, sucrose 50, and chalk 25	25 p.c.	10 to 60 grs. 0.6 to 4 G.	Aromatic, astringent, and antacid
Cretæ Aromat. cum Opio	Aromatic chalk powder 975 G., opium 25 G.	2.5 p.c. (opium)	10 to 60 grs. 0.6 to 4 G.	Aromatic, astringent
Effervescens Co.	Sodium potassium tartrate 7.5 gms., sodium bicarbonate 2.5 gms., mix, and wrap in blue paper: tartaric acid in dry powder 2.5 gms., wrap in white paper	116 & 38½ grs.	193 grs.	Hydragogue cathartic
Glycyrrhizæ Co.	Senna leaf 16, liquorice 16, fennel 8, sublimed sulphur 8, sucrose 52	16 p.c. Senna	60 to 120 grs. 4 to 8 G.	A mild cathartic
Ipecac. et Opii	Ipecac. powder 1, opium powder 1, lactose 8	10 p.c. (opium)	5 to 10 grs. 0.3 to 0.6 G.	Diaphoretic, anodyne
Jalpæ Co.	Jalap 3, acid potassium tartrate 6, ginger 1	30 p.c. Jalap	10 to 60 grs. 0.6 to 4 G.	Hydragogue purgative
Rhei Co.	Rhubarb 25, light and heavy magnesium carbonate, each 32½, and ginger 10	25 p.c. rhubarb	10 to 60 grs. 0.6 to 4 G.	Antacid, stomachic, cathartic
Tragacanthæ Co.	Tragacanth 15, acacia 20, starch 20, and sucrose 45	15 p.c.	10 to 60 grs. 0.6 to 4 G.	Demulcent.

Sera are preparations from serum, containing antitoxic globulins or immune substances having a specific power of neutralising the toxins of the particular organisms against which they have been prepared. There are four in the B.P.

Serum	Preparation	Dose
Antitoxinum Diphthericum	Contains the antitoxin globulins having specific power of neutralising the toxin formed by *Corynebacterium diphtheriæ*	500 to 1000 Units as prophylactic; 10,000 to 20,000 Units as curative
Antitoxinum Tetanicum	Contains the antitoxic globulins having specific power of neutralising the toxin formed by *B. tetani*	1000 to 2000 Units (prophylactic); 20,000 to 40,000 Units (therapeutic)
Antitoxinum Welchicum	Contains the antitoxin globulins having specific power of neutralising the toxin of *B. perfringens*	4000 Units (prophylactic); 10,000 to 20,000 Units (therapeutic) intravenously
Antidysentericum (Shiga)	Contains the immune substances having specific therapeutic value in *B. dysenteriæ* (Shiga)	4000 to 10,000 Units by injection

Spiritus. Spirits.—A spirit, as ordinarily understood, is a distilled product obtained from fermented vinous liquors. But the B.P. spirits, with the exception of Industrial Methylated Spirit, are alcoholic solutions of volatile oils and ethers. They can be divided into two classes —**simple** and **compound**. The simple spirits are solutions of essential oils, ether and chloroform in alcohol (90 p.c.), which often get turbid when diluted with water. The compound spirits contain more than one ingredient. The B.P. spirits are seven in number, of which five are simple and two compound. The dose of all simple spirits is **5 to 30 ms. or 0.3 to 2 mils**, except Spirit. Ætheris, **15 to 60 ms. or 1 to 4 mils.**

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Simple Spirits

Spiritus	Composition	Strength	Action
Ætheris	Ether and alcohol (90 p.c.)	33 p.c.	A diffusible stimulant, antispasmodic and carminative
Cajuputi	Oil of cajuput and alcohol (90 p.c.)	1 in 10	Carminative and antispasmodic
Camphoræ	Camphor and alcohol (90 p.c.)	1 in 10	Stimulant and antispasmodic
Chloroformi	Chloroform and alcohol (90 p.c.)	1 in 20	A diffusible stimulant and antispasmodic
Menthæ Pip.	Oil of peppermint and alcohol (90 p.c.)	1 in 20	Carminative and antispasmodic

Compound Spirits

Spiritus	Composition	Strength	Dose	Action
Ætheris Nitrosi	Nitric acid, sulphuric acid, copper and alcohol (90 p.c.). By distillation.	1.25 to 2.5 p.c. ethyl nitrite	15 to 60 ms. 1 to 4 mils.	Diaphoretic, diuretic, antispasmodic
Ammoniæ Aromaticus	Carbonate of ammonia 25 gms., strong solution of ammonia 50 mils., oil of nutmeg 3 mils., oil of lemon 5 mils., alcohol (90 p.c.) 750 mils., and distilled water q.s. 1000 mils.	2.1 to 2.4 p.c. ammonia 1.265 to 1.485 p.c. CO_2	15 to 60 ms. 1 to 4 mils.	Cardiac stimulant, antispasmodic and carminative

Suppositoria.—Suppositories are solid conical-shaped masses containing some active ingredients, for rectal medication. With the exception of the glycerin suppository, all of them are blended with oil of theobroma which melts at 25°C. The melting point may be raised to 37°C. by the addition of white beeswax. They consequently dissolve slowly when introduced into the rectum. They weigh about 15 grains (1 gramme) each, and are made in conical moulds of massive gun-metal. They are seven in number:—

Suppositorium	Composition	Strength in each	Action
Acidi Tannici	Tannic acid	3 grs. or 0.2 G.	A local astringent and styptic
Belladonnæ	Liquid extract of belladonna 2½ ms.	1/60 gr. (alkaloids)	A local anodyne
Glycerini	Gelatin 14 gms., glycerin 70 gms., and distilled water q.s.	70 p.c. (by weight)	Laxative
Iodoformi	Iodoform	3 grs.	A local antiseptic
Morphinæ	Morphine hydrochloride	¼ gr.	A local anodyne
Phenolis	Phenol	1 gr. or 0.06 G.	Antiseptic and a local anæsthetic.
Plumbi c. Opio	Lead acetate and opium	3 grs. and 1 gr.	Anodyne and astringent

Suppositories are used either to produce a local action on the rectum, or on the adjacent pelvic organs such as the uterus and the bladder, or to produce their general effect on the system after absorption. Thus morphine suppository may be used either to soothe pain and irritation in the rectum or pelvic organs, or to induce sleep.

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Syrupi.—Syrups are fluid preparations of drugs containing a sufficient quantity of sucrose, either to preserve them or to make their administration more agreeable. The dose of all syrups is from 30 to 120 ms., except that of squill and Easton's syrup which are given in 30 to 60 ms. They are twelve in number. If the concentration of sucrose is less than that in simple syrup, the syrup may undergo fermentation unless some preservative is added.

Syrupus	Composition	Strength	Action
Syrupus	Sucrose 667 G., water q.s. to 1000 G.	.....	A sweetening agent
Aurantii	Tincture of orange 125 mils, syrup q.s. to 1000 mils.	1 in 8	A flavouring agent
Ferri Iodidi	Iron 19 G., iodine 58 G., acid. hypophos. dil. 10 ml., water q.s., syrup q.s. to 1000 ml.	5 p.c. ferrous iodide	Hæmatinic tonic
Ferri Phosphatis Co.	Iron 4.3 G., phosphoric acid 48 ml., calcium carb. 13.6 G., potassium bicarb. 1 G., sod. phosph. 1 G., cochineal 3.5 G., sucrose 700 G., orange-flower water 50 ml., water q.s. 1000 ml.	0.9 p.c. ferrous phosph. 1.4 p.c. tricalcium phosph.	Do.
Ferri phosph. c. Quin. et Strychnina	Iron 8.6 G., phosphoric acid 40 ml., strychnine hyd. 0.3 G., quinine sulph. 14.8 G., syrup 560 ml., glycerin 140 ml., water q.s. to 1000 ml.	1 gr. ferrous phosphate, $^4/_5$ gr. of Quin. sulph. and $^1/_{60}$ gr. of strychnine in 1 dr.	A general and nervine tonic Hæmatinic
Glucosi Liq.	Glucose liquid 333 G., syrup 667 G.	1 in 3	An excipient for pills
Limonis	Lemon peel 60 G., alcohol (60 p.c.), q.s., citric acid 24 G., syrup q.s. to 1000 ml.	6 p.c.	A flavouring agent
Pruni Serotinæ	Wild cherry bark 15 G., sucrose 80 G., glycerin 5 ml., water q.s. to 100 ml.	15 p.c.	A sweetening agent
Scillæ	Vinegar of squill 45 mils., sucrose 80 gms., water q.s. to 100 mils.	4.5 p.c. squill	Expectorant and emetic
Sennæ	Liquid extr. of senna 250 ml., oil of coriander 1.5 ml., sucrose 700 G., water q.s. to 1000 ml.	25 p.c.	A mild cathartic
Tolutanus	Balsam of tolu 25 gms., sucrose 660 gms., and water q.s. to 1000 gms.	2.5 p.c.	A sweetening agent for cough mixtures
Zingiberis	Strong tincture of ginger 5 ml., syrup q.s. to 100 ml.	5 p.c.	Carminative and antispasmodic

Tabellæ. Tablets.—According to the B.P. tablets are small flat pieces of chocolate containing minute doses of medicinal agents. Tablet preparations are very popular now, but are often useless, since when made by compression, they may become so hard and insoluble as to be recovered quite undissolved from the fæces. According to their mode of preparation, they may be divided into three classes, viz.:—(1) those made by compression; (2) those made without compression but by moulding, commonly known as tablet-triturates; and (3) those prepared from a chocolate basis, as ordered by the B.P. The manufacture of compressed tablets has developed into a special industry in practical pharmacy and is done by special machinery.

There is only one tablet in the B.P., viz.:—

Tabella Glycerylis Trinitratis.—Made of chocolate, each weighing 5 grains (0.3 gm.) and containing $^1/_{120}$ gr. (0.0005 G.) of glyceryl trinitrate. *Dose.*—1 or 2 tablets.

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Tincturæ.—Tinctures are alcoholic solutions containing all the active ingredients of the drugs of which they are compounded. In this respect they differ from the official spirits which are merely alcoholic solutions of essential oils. They are prepared either by (*a*) *maceration*, (*b*) *percolation*, or (*c*) *simple solution*. They are thirty-three in number; of these, only one is from the animal kingdom, viz. :—Tr. Cocci.

Alcohol of various strengths is used to make tinctures, such as alcohol (90 p.c.), alcohol (70 p.c.), alcohol (60 p.c.) and alcohol (45 p.c.).

One tincture is made with ether, viz., Tr. Lobeliæ Ætherea. The total bulk for all tinctures is 1000 mils with alcohol, or with alcohol and water. The quantities given are for 1000 mils.

Some preparations which were formerly grouped under tinctures are now known as Liquors, being simple solutions of chemical substances. They are liquor iodi fortis and mitis, liquor quininæ ammoniata, liquor ferri perchlor.

Twenty-four tinctures are "Simple" having only one ingredient and one solvent. Five tinctures are called "Compound," having more than one ingredient. Another group of four tinctures are not called compound in the B. P. though they contain more than one ingredient and a solvent. They may more appropriately be named "Complex."

We shall group the Tinctures under three heads, viz. :—(1) **Simple**, (2) **Compound**, and (3) **Complex.**

SIMPLE TINCTURES

Tinctura	Ingredients	Alcohol p.c. in Menstruum	Process	Strength	Dose
Asafœtidæ	Asafetida 200 G.	70	M.	20 p.c.	30 to 60 ms.
Aurantii	Fresh bitter peel 250 G.	90	M.	25 p.c.	30 to 60 ms.
Belladonnæ	Belladonna leaf 100 G.	70	P	0.03 p.c. alkaloids	5 to 30 ms.
Calumbæ	Calumba 100 G.	60	M.	10 p.c.	30 to 60 ms.
Capsici	Capsicum 50 G.	60	M.	5 p.c.	5 to 15 ms.
Cinchonæ	Extract of Cinchona 100 G.	70	S.	1 p.c. alkaloids	30 to 60 ms.
Cocci	Cochineal 100 G.	45	M.	10 p.c.	5 to 15 ms.
Colchici	Liquid extract 100 ml.	60	S.	0.03 p.c. colchicine	5 to 15 ms.
Digitalis	Leaf 100 G., or powdered leaf 100 G.	70	P.	6 Units in 90 ms.	5 to 15 ms. or 30 to 90 ms.
Hyoscyami	Liquid extract 100 ml.	70	S.	0.005 p.c. alkaloids	30 to 60 ms.
Krameriæ	Krameria 200 G.	60	P.	20 p.c.	30 to 60 ms.
Limonis	Lemon peel 250 G.	60	M.	25 p.c.	30 to 60 ms.
Lobeliæ Ætherea	Lobelia 200 G., spt. ether q.s. to 1000 ml.	—	P.	20 p.c.	5 to 15 ms.
Myrrhæ	Myrrh 200 G.	90	M.	20 p.c.	30 to 60 ms.
Nucis Vomicæ	Liquid ext. 83.4 ml., alcohol 500 ml, water to 1000 ml.	90	S.	0.125 p.c. strychnine	10 to 30 ms.
Opii	Opium 200 G., alcohol q.s., water q.s. to 1000 ml.	90	S.	1 p.c. morphine	5 to 30 ms.
Quassiæ	Quassia 100 G.	45	M.	10 p.c.	30 to 60 ms.
Quillaiæ	Quillaia 50 G.	45	P.	5 p.c.	30 to 60 ms.
Scillæ	Squill 100 G.	60	M.	10 p.c.	5 to 30 ms,
Senegæ	Liquid extract 200 ml.	60	S.	20 p.c.	30 to 60 ms.
Stramonii	Stramonium 200 G.	45	P.	0.025 p.c. alkaloids	5 to 30 ms.
Strophanthi	Strophanthus 100 G., alcohol 500 ml. or q.s.	70	P.		2 to 5 ms.

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Tinctura	Ingredients	Alcohol p.c. in Menstruum	Process	Strength	Dose
Tolutana	Balsam of tolu 100 G.	90	S.	10 p.c.	30 to 60 ms.
Zingiberis Fortis	Ginger 500 G.	90	P.	50 p.c.	5 to 10 ms.
Zingiberis Mitis	Strong tincture of ginger 200 ml.	90	S.	.....	30 to 60 ms.

Compound Tinctures

Tinctura	Ingredients	Alcohol p.c in Menstruum	Process	Strength	Dose
Benzoini Co.	Benzoin 100 gms., storax 75 gms., tolu 25 gms., aloes 20 gms.	90	M.	1 in 10	30 to 60 ms. 2 to 4 mils.
Cardamomi Co.	Cardamom 14 gms., caraway 14 gms., cinnamon 28 gms., cochineal 7 gms., glycerin 50 mils	60	P.	1.4 p.c.	30 to 60 ms. 2 to 4 mils.
Cinchonæ Co.	Ext. of cinchona 50 gms., bitter orange peel 50 gms., cochineal 3 gms., serpentary 25 gms.	70	P.	1/4 gr. alkaloids in 60 ms.	30 to 60 ms. 2 to 4 mils.
Gentianæ Co.	Gentian 100 gms., bitter orange peel 37 1/2 gms., cardamom seeds 12 1/2 gms.	45	M.	1 in 10	30 to 60 ms. 2 to 4 mils.
Rhei Co.	Rhubarb 100 gms., cardamom, coriander each 12 5 gms glycerin 100 mils.	60	P.	10 grs. in 110 ms.	30 to 60 ms. 2 to 4 mils.

Complex Tinctures

Tinctura	Ingredients	Alcohol p.c. in Menstruum	Process	Strength	Dose
Catechu	Catechu 200 gms., cinnamon 50 gms., alcohol q.s. to 1000 mils.	45	M.	1 in 5	30 to 60 ms. 2 to 4 mils.
Ipecacuanhæ	Liquid extract 50 ml., alcohol 200 ml., glycerin 200 ml., water to 1000 ml.	90	S.	0.1 p.c. alkaloids	10 to 30 ms. or 1 1/2 to 1 oz. emetic.
Opii Camphorata (Tr. Camphoræ Co.)	Tr. opii 50 ml., benzoic acid 5 G., camphor 3 G., oil of anise 3 ml., alcohol q.s. 1000 ml.	60	S.	0.05 p.c. morphine	30 to 60 ms. 2 to 4 mils.

Note—M = Maceration. P = Percolation. S = Solution.

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Tinctura	Ingredients	Alcohol p.c. in Menstruum	Process	Strength	Dose
Valerianæ Ammoniata.	Valerian powder 200 gms., oil of nutmeg 3 mils., oil of lemon 2 mils., dilute ammonia solution 100 mils., alcohol 900 mils.	60	M.	1 in 5	30 to 60 ms. 2 to 4 mils.

The following tinctures are standardised :—

Tr. belladonnæ, cinchonæ, cinchonæ co., colchici, hyoscyami, ipecacuanhæ, nucis vomicæ, opii, opii camphorata, stramonii are standardised by chemical assay.

Tinctures of digitalis and strophanthus are standardised by biological assay.

The dose of most Tinctures is from 30 to 60 ms., except

Ipecacuanha and nux vomica,	10 to 30 ms.
Belladonna, opium, squill and stramonium,	5 to 30 ms.
Capsicum, cochineal, digitalis and lobelia	5 to 15 ms.
Ginger (strong)	5 to 10 ms.
Strophanthus	2 to 5 ms.

The dose of tincture of digitalis when given in a single dose is 30 to 90 ms.

Toxins are three in number

Toxinum	Preparation	Dose
Diphthericum Calefactum (Schick Control)	Schick test toxin heated to a temperature not less than 70° for not less than 5 minutes.	3 ms. by intradermal injection.
Diphthericum Detoxicatum	A sterile filtrate from a culture on nutrient broth of *Corynebacterium diphtheriæ*	By subcutaneous injection the volume indicated on the label as the dose, on 2 or 3 occasions, at intervals of 2 to 4 weeks.
Diphthericum Diagnosticum (Schick Test Toxin)	Prepared from a culture on nutrient broth of *Corynebacterium diphtheriæ*	3 ms. by intradermal injection.

Trochisci.—Troches or **Lozenges** are flat solid tablets composed of a basis and one or more active drugs uniformly divided, for the purpose of slowly melting in the mouth. The quantities given are for 1000 lozenges. The new B.P. has the following for the preparation of their bases :—

Take 1000 times the quantity of the drug ordered for one lozenge; dissolve such salts of alkaloids as may be ordered in 20 mils, or a sufficient quantity of distilled water; mix the solution with 1000 gms. of sucrose and 70 grms. of acacia, both finely powdered. Incorporate 20 mils of tincture of tolu, and any other drugs ordered. Make into a paste with sufficient distilled water; divide into 1000 equal lozenges, dry at a moderate temperature.

Note—M=Maceration. P=Percolation. S=Solution.

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Trochiscus	Ingredients	Strength in each	Action and uses
Acidi Tannici	Tannic acid 30 gms.	1/2 gr.	A local astringent.
Bismuthi Comp.	Bismuth carb. 150 G., heavy magnes. carb. 150 G., cal. carb. 300 G., acacia 70 G., sucrose 1000 G., oil of rose 0.05 ml., water q.s.	2 1/4 gr. 2 1/4 gr. 4 1/2 gr.	Antacid
Krameriæ	Extract of krameria 60 gms.	1 gr.	Astringent
Krameriæ et Cocainæ	Extract krameria 60 gm., cocaine hydrochloride 3 gm.	1 gr. 1/20 gr.	Astringent and anæsthetic
Morphinæ et Ipecacuanhæ	Morphine hydr. 2 G., powdered ipecac. 6 G.	1/32 gr. 1/10 gr.	Allays cough
Phenolis	Liquefied phenol 35.5 mils., acacia 90 G., tragacanth 30 G., citric acid 7 G., carmine 3 G., sucrose 1000 G., water q.s.	1/2 gr.	Antiseptic

Unguenta.—Ointments are semisolid or soft preparations for external application containing some active drugs mixed with a fatty, oily or paraffin basis. Lard, either plain or benzoinated, glycerin, prepared suet, beeswax, etc., either alone or in combination, form the basis of all B.P. ointments.

There are nineteen ointments in the B.P. They may be divided into two classes, viz.—(1) General, and (2) Mercurial.

General Ointments

Unguentum	Composition	Strength	Action and uses
Acidi Borici	Boric acid 1, white paraffin ointment 9	1 in 10	Antiseptic
Acidi Salicylici	Salicylic acid 2, white paraffin ointment 98	1 in 50	Antiseptic
Acidi Tannici	Tannic acid 20, glycerin 20, yellow beeswax 12, benzoinated lard 48	20 p.c.	Astringent
Aquosum	Borax 10 G., water 240 ml., white beeswax 125 G., white soft paraffin 125 G., olive oil 500 ml.	24 p.c.	Antiseptic, emollient
Capsici	Capsicum 25 gms., hard paraffin 10 gms., soft paraffin 75 gms., lard 10 gms.	1 in 4 1/2	Rubefacient
Chrysarobini	Chrysarobin 4, simple ointment 96.	1 in 25	Antiparasitic and stimulant application for psoriasis
Paraffini	White beeswax 20 G., hard paraffin 80 G., white or yellow soft paraffin 900 G.	.....	A basis for ointment (demulcent)
Phenolis	Phenol 30, white beeswax 75, lard 50, hard paraffin 75, white soft paraffin 770	3 p.c.	Antiseptic
Simplex	Wool fat 50, hard paraffin 100, white or yellow soft paraffin 850	.....	Basis for ointment
Sulphuris	Sublimed sulphur 1, simple ointment 9	1 in 10	Antiparasitic. Cures scabies
Zinci Oleatis	Zinc sulphate 30 gms., hard soap shavings 90 gms., boiling water and white soft paraffin, of each q.s.	50 p.c. oleate	A mild astringent for eczema
Zinci Oxidi	Zinc oxide 15, simple ointment 85	15 p.c.	Mild astringent

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MERCURIAL OINTMENTS

Unguentum	Composition	Strength	Action and uses
Hydrargyri	Mercury 30, benzoinated lard 65, suet 5	30 p.c.	Resolvent, antiparasitic
Hydrargyri Ammoniati	Ammoniated mercury 50, simple ointment 950.	1 in 20	Antiparasitic. Destroys pediculi
Hydrargyri Comp.	Mercury ointment 40, yellow beeswax, olive oil, each 24, camphor 12	12 p.c. of mercury	Absorbent, useful in glandular enlargement, etc.
Hydrargyri Nitratis Dilutum	Mercuric nitrate ointment 2, yellow soft paraffin 8	1 in 5	Same as above. Invaluable in eczema, tinea tarsi
Hydrargyri Nitratis Fort.	Mercury 1 gm., nitric acid 3 mils., lard 4 gms., olive oil 7 gms.	6.7 p.c. of mercury	A local alterative, astringent and stimulant
Hydrargyri Oleati	Mercuric oleate 25, simple ointment 75	25 p.c.	Same as Ung. Hydrarg.
Hydrargyri Subchloridi	Mercurous chloride 20, simple ointment 80	20 p.c.	Antisyphilitic, alterative and resolvent

Vaccina. Vaccines. Three in number as under

Vaccinum	Preparation	Dose
Tuberculinum Pristinum	The concentrated filtrate from a fluid medium on which B. tuberculosis has been grown	1/60 to 1/12 minim. (diagnostic); 1/6000 min. gradually increased (by subcutaneous injection)
Typho-paratyphosus	Sterile suspension of B. typhosus, B. paratyphosus A & B which have been killed by heat	1st dose 0.5 ml. 2nd dose 1.0 mil after 7 to 10 days, subcutaneously,
Vacciniæ	A preparation of the substance obtained from the vesicles produced by inoculation of vaccinia virus on the skin of healthy animals	1 minim by scarification.

NON-OFFICIAL OR NON-PHARMACOPŒIAL PREPARATIONS

Balnea. Baths.—The immersion of the whole or a part of the body in some liquid or vapour is called a bath. It is said to be general when the whole body is brought under its influence, and local when a part only.

Properly speaking, only medicated baths come under non-official preparations; but a description of the different kinds of medicated and non-medicated baths will be given here.

A. Cold Bath.—Temperature 35° to 70° F. Average 50° to 60° F. It has a powerful tonic action, increasing digestion, metabolism and body weight; but in order to obtain these effects the bath should not be continued long after the primary reaction has set in. If it is prolonged it may cause secondary depression followed by delayed reaction. In fevers, it abstracts heat, and thereby lessens tissue change and prevents complications; hence it is very useful in hyperpyrexia of

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rheumatism, typhus, typhoid, and **remittent fevers,** and **pneumonia.** The bath must be repeated if the temperature rises. There are several ways of using a cold bath. The following are a few examples:

1. **Cold Affusion.**—In which 5 to 6 gallons of cold water are thrown over the body. It is valuable for resuscitating persons from **syncope, narcotic poisoning, convulsions, sunstroke, hysteria,** etc.

2. **River Bath.**—Bathing in the river is more invigorating than a full cold bath either in a tub, reservoir, or a tank. It stimulates digestion, gives tone to the system and strengthens muscles, especially if it is accompanied by swimming, or if the current of the water is very strong.

3. **Cold Shower Bath** is an effective **tonic,** being useful in **mania, hysteria, sunstroke,** etc. **Needle Bath** is a shower bath thrown in a fine spray.

4. **Cold Sitz-Bath or Cold Hip-Bath.**—In this the person sits in a tub with the water up to his hips. The vessels of the cooled surface and intestines first contract and then dilate, especially when friction is applied.

5. **Cold Foot-Bath** tones the system and strengthens the feet, but is to be avoided during the menstrual period.

6. **Cold Wet-Sheet Pack** is done thus:—Spread two blankets over the bed taking care to cover the pillow. Thoroughly wet a bed-sheet and spread it over them. Strip the patient naked and make him lie flat on the sheet. Wrap him up tightly in the sheet and blankets, the ends of the sheet being carefully tucked in on each side and the feet covered. Cover him with two or more blankets, the face being left open. After a short feeling of chilliness the patient experiences a delightful glow followed by copious perspiration, thereby reducing the temperature, delirium, and irritability. After ½ to 1 hour the packing is removed and the body well rubbed with dry towels.

Instead of cold, tepid or warm water may be substituted. The above description applies to **general packing,** which is usefully employed in **specific fevers,** such as measles, scarlatina, small-pox, etc., to help the development of the rash, or to bring it out if it has receded. To reduce **delirium, excitement,** and **hyperpyrexia,** and in **mania** and **insomnia,** it is always useful. A **local wet pack** can be used in pneumonia, chronic diarrhœa, etc. A **cold compress** round the throat checks the inflammation of acute tonsillitis, whilst a similar compress on the stomach will often check obstinate vomiting.

7. **Cold Douche.**—In this a single stream of water is forcibly directed against a part of the body. Its effects depend mainly upon the size, height, and temperature of the stream, as well as the extent of the surface affected. The douche can be usefully directed against (*a*) *head,* in alcoholic coma and narcotic poisoning; (*b*) the *spine,* in spermatorrhœa, melancholia, and general debility; (*c*) *liver* and *spleen,* for chronic congestion and enlargement; (*d*) the *joints,* for chronic inflammation and stiffness; (*e*) the *perinæum,* in which case an **ascending douche** with a rose is used in pruritus ani, hæmorrhoids and spermatorrhœa; (*f*) the *vagina* in leucorrhœa; (*g*) *rectum,* in constipation and hæmorrhage.

8. **Cold Sponging.**—In this the surface of the body is freely sponged over while the patient is sitting or standing on a shallow tub. It has a tonic and bracing effect.

9. **Ice Bag and Leiter's Coil.**—For local application of cold to the [illegible], chest, or abdomen, an india-rubber bag filled with ice or a closely wound coil of metal tubing through which a continuous stream of water is allowed to flow may be applied.

10. **A Freezing Mixture** consisting of powdered ice 2 parts, common salt 1 part, is very useful in minor operations and in chronic rheumatism. It causes anæsthesia and may vesicate if left too long in contact with the skin.

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B. Warm or Hot Bath.—It may be either *medicated* or *non-medicated*, general or local. It (*a*) softens the dermis and liquefies the fatty secretions and hence acts as a good **detergent** in many scaly and scabby skin diseases; (*b*) stimulates local circulation and lessens that of the internal organs, whereby relieves pain of intestinal, biliary, and renal colics; (*c*) relaxes tissues and relieves muscular spasms in urethral stricture, colic, laryngeal spasm, hernia, infantile convulsions, etc.; and (*d*) stimulates the secretion of sudoriferous glands, by which many kidney diseases are benefited and uræmia may be averted.

Great care should be taken during and after a hot bath. The patient must be quickly dried, covered, and put in a warm bed. A cup of hot tea, hot milk, or hot water greatly helps diaphoresis.

1. **Tepid Bath.**—Temp. 85° to 95° F. it has a detergent, sedative and antipyretic effect. Useful in pyrexia and restlessness.
2. **Warm Bath.**—Temp. 95° to 100° F. Used in fevers, threatening inflammatory affections, etc., as bronchitis, pneumonia.
3. **Hot Bath.**—Temp. 100° to 106° F. Action is the same as above, but more powerful.
4. **Hot Foot-Bath.**—To arrest threatened catarrh, cold in the head, epistaxis, infantile convulsion and to restore menstrual flow stopped by cold.
5. **Hot Sitz-bath.**—Useful in amenorrhœa, dysmenorrhœa, sudden cessation of menstruation from cold, dysuria, cystitis, etc. The addition of a little **mustard** helps to re-establish the menstrual flow more quickly.
6. **Hot-water Sponging.**—Sponging the head, temples, and neck with hot water relieves the headache in influenza, catarrh, and other diseases.
7. **Hot Douche.**—A very hot uterine douche, temperature between 110° and 115° F. is a good method for checking post-partum hæmorrhage.

C. **Medicated Baths.**—In these, medicinal agents are dissolved in cold or warm water. They may be divided into the following:—

1. **Sea Bath.**—On account of the various saline ingredients held in solution, sea-bathing is especially invigorating and stimulating to the skin. Moreover, the temperature being more or less uniform, sea-bathing is more easily borne by the weak than river-bathing.
2. **Carbonic Acid Bath.**—This is a stimulating saline bath containing sodium chloride 3 p.c., calcium chloride 1 p.c., carbonic acid gas (free) up to 3 grammes to 1 litre. Recommended in heart disease either functional or organic. The effect of the **Nauheim Bath** is due to its saline and gaseous constituents.
3. **Acid Bath.**—In this a flannel roller 1 foot broad is soaked in a bath containing diluted nitro-hydrochloric acid 8 ozs. in 1 gallon of water at 98° F., and wrapped twice round the hepatic region, after wringing out the superfluous lotion. It is then completely covered by a piece of oiled silk leaving a little margin. The bath should be renewed morning and evening and worn for days. Useful in hepatic disorders.
4. **Alkaline Bath** is made by dissolving crystallised sodium carbonate (1 dr. to 1 gal.) in water, and is useful in removing scabs and scaly incrustations.
5. **Mustard Bath** (½ to 1 dr. in 1 gallon).—A powerful stimulant to the skin, used to quicken the appearance of exanthematous eruptions. The patient should remain in the bath from 5 to 10 minutes.
6. **Bran Bath.**—Bran 4 lbs. are boiled in water 1 gallon, and strained. This liquor is added to water sufficient for a bath. It removes irritation of the skin.
7. **Neem Bath.**—It is prepared by adding the decoction of leaves of *Melia azadirachta* to the ordinary bath. It may be general or local, and is largely employed in India in various skin diseases.

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8. **Mineral Water Bath.**—A course of baths in any of the spas has special advantages. The effects of a bath in simple thermal water are similar to those derived from an ordinary warm bath; but they differ according to the composition of the mineral waters. Thus, bathing in and drinking sulphur water are very efficacious in chronic rheumatism, gout, hepatic congestion, etc.

D. Vapour Bath.—This may be aqueous or medicated. A **Steam Bath** may be made by boiling water over a spirit-lamp under a cane-bottomed chair, on which the patient sits, enveloped completely, except the head, by one or two blankets. Action and uses are the same as those of hot water bath. The **Russian Bath** consists in exposure of the body to moist vapour at different temperatures. It is said to be risky to persons with weak hearts, and there is certainly more danger of heat stroke than in the **Turkish Bath**, in which only dry air is used. Either of these baths is useful in rheumatism, gout, malaria, renal and skin diseases.

SCALE OF TEMPERATURES OF BATHS (Startin)

Bath	Water	Vapour	Hot Air
Cold	33° to 65° F.		
Cool	65° to 75° F.		
Temperate	75° to 85° F.		
Tepid	85° to 92° F.	90° to 100° F.	96° to 106° F.
Warm	92° to 98° F.	100° to 115° F.	106° to 120° F.
Hot	98° to 112° F.	115° to 140° F.	125° to 170° F.

E. Air Bath.—**Hot-air bath** may be employed like a steam bath, by simply arranging a few electric bulbs connected by wires inside the frame-work which supports the bed clothes, or by passing hot air.

Bolus.—A bolus is a large pill containing over 10 grains of powdered ingredients. The most convenient plan when a large dose of a nauseous powder is to be administered, is to give it in a cachet, or wafer paper.

Buginaria.—**Bougies** are elongated cylindrical preparations containing active drugs mixed with the suppository basis for introduction into the urethral and the nasal cavities. Bougies are made like suppositories but differ from them in shape.

Antrophores are medicated bougies containing a spiral spring wound with fine wire, and coated first with an insoluble layer of white gelatin and then with a diluted mucilage. They may be medicated with cocaine, iodoform, protargol, etc.

Cachets are wafer-paper capsules. They consist of two concave or watch-glass shaped halves or discs of wafer-paper stuck together at the rims by moisture. Any nauseous or bitter drug can be thus enclosed between the two halves and swallowed without being tasted. Cachets should be dipped in water immediately before swallowing.

Capsules.—A capsule is a gelatin sac enveloping a dose of some nauseous or disagreeable drug.

Carbasa Antiseptica.—**Antiseptic Gauzes** are mulmuls steeped in some antiseptic solution and dried afterwards. The following is the process for an extemporaneous preparation. Take 2 yards of gauze having 30 threads to the linear inch, hang it over a string, and spray over it uniformly the required volume of antiseptic solution on each side, turning once or twice until the whole of it is used. Or the folded gauze may be dipped into the solution in a deep dish, and turned over and over until the whole of it is equally absorbed and then taken out, unfolded, dried and sterilised.

Collunaria are lotions used as nasal douches.

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Collutories are throat or mouth paints; as Glycerinum Acidi Borici. Collutoire is a French term.

Collyria are eye-lotions or eye-washes. Sometimes they are called eye-drops.

Cremora.—Creams are soft or semi-liquid preparations for external application; having glycerin, soft paraffin or some similar substances as a basis, *e.g.* Cold Cream.

Elæosacchara. Aromatic Sugars or Oil Sugars.—These are more common on the Continent than in England, and are made by triturating 9 minims of volatile oils to 1 oz. of sugar. They are used as flavouring agents.

Enemata. Enemas. Clysters. Lavements. Rectal Injections.—A liquid preparation introduced into or through the rectum by means of a suitable instrument is called an enema.

If the injection is meant to evacuate the bowels, 1 to 2 pints of liquid are injected, the patient lying on his left side; but when it is intended that it should be retained, a small quantity—2 to 4 ozs. should be used. If it is considered desirable to introduce 3 to 6 pints, the liquid must be slowly thrown up the bowel while the patient is lying first on his left, then on his right side with his pelvis raised, or, if necessary on his knees and elbows, pressing the anus with a towel whenever there are expulsive cramps. This is best done by slowly pouring the fluid into a funnel to which a long gum-elastic tube is attached. It then flows steadily as the result of hydrostatic pressure and is less likely to be ejected. This process is called **Enteroclysis.** It must be borne in mind that the process of injection should be carried on slowly and with occasional pauses, otherwise the enema will be expelled by premature contraction of the intestine. The temperature of the liquid should be 98° F. Cold water is soon rejected.

The following are the chief varieties of enemas with their uses:—

1. **Anthelmintic Enemata** are chiefly used to expel thread-worms, e.g. infusion of quassia, or hypertonic saline.

2. **Antispasmodic Enemata.**—For this purpose an injection of Oil of Turpentine, Asafetida (Tr. asafœtida 6 to 12 p.c. in mucilage of starch). Bromides (pot. bromide 1 p.c. with acetyl salicylic acid 0·5 p.c., and mucilage tragacanth, in normal saline), etc., is given when the intestine is distended with flatus, or getting cramped.

3. **Astringent Enemata.**—These are used for checking diarrhœa, rectal hæmorrhage, and mucus discharge from the rectum and lower bowels.

4. **Emollient Enemata.**—A decoction of starch, linseed, or barley soothes the irritable mucous membrane of the rectum and colon.

5. **Sedative Enemata.**—These are used in painful affections of the rectum, e.g. Tr. opii 0·5 to 6 p.c. in mucilage of starch.

6. **Purgative Enemata.**—These are often resorted to when the lower bowels are to be evacuated. Ordinarily, for an adult 1 pint, for a child of four years of age 4 to 6 ozs., and for an infant 1 oz., are enough. Soap and warm water, thin gruel, and castor oil or olive oil, etc., are often used for this purpose. Glycerin 2 to 4 drs. with an equal amount of warm water injected by means of a suitable syringe, or a glycerin suppository introduced into the rectum, evacuate the bowels speedily.

7. **Nutrient Enemata.**—In case where food cannot be swallowed by the mouth, or retained by the stomach, liquid glucose or dextrose 10 p.c. with normal saline may be given per rectum, not more than 4 oz. at a time. Before the nutrient enema is given the bowel should be washed out each *morning with tepid water.*

Fomenta.—Fomentations consist of flannels, cloths, or sponges wrung out of hot water to which a drug may or may not have been added, for application to the surface of the body.

The proper way to apply fomentations is to take a twofold piece of

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flannel large enough to cover the affected part. Immerse this folded flannel in a a kettle of boiling water or pour boiling water over it in a basin, and lift it by a pair of tongs or a stick, and put it on a wringer—a stout towel or duster with sticks attached to both ends. The water is then squeezed out as much as possible and the flannel applied to the affected part and covered with a large piece of india-rubber sheeting or oiled silk, extending about an inch beyond the flannel. Place over this a thick layer of cotton-wool and bandage. If the full effect of fomentation is desired the flannel should be changed every 20 or 30 minutes. In the case of the feet, hands or forearms, dipping them in hot water may do, but its temperature should be maintained by frequent small additions of boiling water.

If it is desired to produce a counter-irritation, oil of turpentine may be sprinkled over the flannel before application. This forms the **turpentine-stupe.** For an anodyne or sedative action, laudanum may be sprinkled in the same way, or a few poppy-heads or a little opium may be put into the water before boiling.

Dry fomentation is made by filling bags with hot bran, salt, sand, or chamomile flowers. Bottles filled with hot water and covered with flannel bags or old stockings may be used for dry fomentation. A piece of flannel roasted over fire and applied also serves the purpose.

Hot Antiseptic Compresses.—These consist of folds of lint or cloth soaked in hot antiseptic lotions and covered with a piece of water-proof, oiled silk, or guttapercha tissue ; as Boric Acid Compress.

Fumigation is a local or general bath of volatilised drugs. Sulphur and mercury are chiefly used for this purpose. Mercurial fumigation, either *general* or *local*, has long been used in the treatment of secondary syphilis.

Gargarismata. Gargles.—A gargle is a liquid preparation used for topical action on the mouth, throat, and pharynx. A gargle may be any of the following kinds :—

1. **Stimulant Gargle**, that stimulates the mucous membrane and glands : as Capsicum (Tr. Capsicum 2 drs. to Water 8 ozs.), Myrrh, Eucalyptus Gum (2 drs. to 8 ozs.), etc. These gargles often relieve deafness due to obstruction of the eustachian tube by increased pharyngeal secretion.

2. **Astringent Gargle**, that checks excessive secretion ; as iron salts, zinc salts, alum (12·5 p.c.), tannic acid (½ dr. to 8 ozs.), astringent infusions, etc.

3. **Antiseptic Gargle**, that removes foul secretions and odours; as carbolic acid (5 p.c.), boric acid, potassium permanganate (0·025 p.c.), etc.

4. **Demulcent Gargle**, that removes burning and irritation ; as barley water, linseed tea, ispaghul seed tea, milk, etc.

Gossipia Antiseptica.—Antiseptic Cottons are made by charging absorbent cotton-wool with various antiseptic drugs. This is done by soaking cotton in some saturated antiseptic fluid and afterwards drying it ; as Gossip. Acidi Borici, Gossip. Acidi Salicylici, etc.

Guttæ.—Drops are liquid preparations used as drops ; as eye-drops, drops for the ear, etc.

Haustus. Draught.—A liquid preparation or mixture when taken in a single dose is called a draught ; as castor oil draught ; hydrate of chloral draught, etc.

Insufflations are powders blown into the throat, nostrils, or larynx. Laryngeal insufflation can be managed thus :—A vulcanite tube curved at a suitable angle, having an aperture covered by a slide, through which the medicinal powder is introduced, is carried over the tongue to the laryngeal orifice, and the powder is either blown in by the mouth or by an elastic bulb attached to the end of the tube. This instrument is called "Pulverflator." A quill or a tube half filled with powder and blown by the mouth may do for nostrils and throat.

Jujubes are lozenges made of gum acacia and sugar. They are

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prepared by boiling to a suitable consistence, gum acacia 16 lbs., sugar 7 lbs. and water ½ gal. They are sometimes covered with a coating of crystallised sugar.

Linctus.—**Lincture** or **Loch** is a thin confection to be slowly swallowed in small doses, so as to act on the throat. The basis of linctus is either treacle, syrup, honey, or any other sweet viscid substance. When powders are the active ingredients they should be made very fine, before admixture with the basis.

Massæ.—**Masses** consist of ingredients mixed together to the consistence of a pill. They are official in the U.S.P.

Mollinum is an ointment prepared with mollin or superfatted soap. It is easily washed off with water forming a lather and leaves the skin fresh and supple. As Mollinum Hydrargyri. Mollin contains 17 p.c. of uncombined fat and 30 p.c. of glycerin.

Nebulæ are solutions of drugs in aqueous, oily, alcoholic, or glycerinated media to be sprayed into the throat by the help of a spray-producer; as Nebula Adrenalini et Cocainæ.

Opodeldocs or **Saponimenta** are preparations having as their basis soap liniment. Medicated opodeldocs are official in Continental Pharmacopœias.

Pastillus or **Pastil** is a soft jujube variously medicated, having glycogelatin as its basis instead of gum acacia and sugar. These are used like lozenges. As Pastilli Mentholis.

Perles are minute pills.

Pessi.—**Pessaries** resemble suppositories, but are intended for introduction into the vagina.

Pigmenta.—**Paints** are liquid preparations used for application to the throat, skin or other parts. A pigment differs from a collutoire in that the former is used as a paint for any part of the body, whereas the latter is for brushing the throat or mouth only. As Pigmentum chrysarobini, Pigmentum Iodoformi Co.

Sprays are liquid preparations intended for application to the upper air passages through an atomizer.

Steatina.—**Steatins. Ung. Extensa** or **Salve Mulls** are ointments of a hard consistence spread on muslin, and capable of being folded and cut at pleasure. Mutton or beef suet form their principal basis.

Sticks or **Pencils** are solid cylindrical rods prepared by fusing drugs and pouring the melted mass into suitable moulds; as toughened and mitigated caustics. When the melted mass is poured into a conical mould it is called a cone; as a Menthol Cone.

Styles are thin bougies about 2 inches long for introduction into the lachrymal sac and nasal duct.

Triturationes.—**Triturations** are solid dilutions. These are intimate mixtures of substances with lactose.

Varnishes are preparations which, when applied to the skin, evaporate and leave a coating. Varnishes are often medicated.

Wafer papers are used to wrap round nauseous or bitter powders to disguise their taste. They are made of flour and water, and become limp when moist. Cachets consist of the same material.

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PART II

ADMINISTRATION OF DRUGS

CHANNELS FOR ADMINISTRATION OF DRUGS

THE following are the various channels through which drugs can be introduced into the system either for their local action or for systemic effects after absorption :—

1. **The Digestive tract** is the most important and the ordinarily selected route.

(*a*) *The Mouth.*—We administer drugs by this route either for their absorption by the alimentary tract, or for their local action. Sometimes drugs produce systemic effect through absorption by the mucous membrane of the mouth. Nitroglycerin is often used by this route, and is more effective than when swallowed, because it avoids the portal circulation. *Sublingual* administration of adrenaline is adopted to avoid decomposition of the drug in the stomach. For local action we use gargles, paints, pastilles, lozenges, etc.

(*a*) *The pharynx* is reached by pigments, pastilles, collutories, sprays, insufflations, lozenges, jujubes.

(*c*) *The Stomach and Intestine.*—Drugs are administered by this route either for their local action on the stomach and intestine, or for their systemic effect after absorption. For local effect on the stomach, digestive ferments, direct emetics, or gastric sedatives are generally used. Purgatives are used for their effect on the intestine and these unfold their action on reaching this part of the gut. Sometimes drugs are administered for action on the intestine and not intended to be dissolved or decomposed in the stomach. Such drugs are administered in keratin coated or salol varnished pills.

But the greatest use of drugs by this route is for their systemic effect after absorption. The absorption of a drug is influenced by (i) its *solubility*, and (ii) the *conditions under which it is administered.* Thus, a pill takes a longer time to be absorbed than a mixture. Again, salines are more rapidly absorbed than metallic salts or alkaloids. A drug acts more rapidly on an empty stomach than on a full one. On an empty stomach with a healthy mucous membrane crystalloids in solution pass readily through the vessel walls. Colloids on the other hand require to be digested and emulsified before they can be taken up by the blood-vessels and the lacteals. Mixtures, draughts, pills, powders, boluses, emulsions and confections are administered by this route.

(*d*) *The Rectum.*—The drugs are sometimes administered by this channel either for action after absorption, or for

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their local action on the bowel, *e.g.*, suppositories, enemas, etc. This route is taken advantage of to introduce nutrients (*e.g.*, glucose), and saline solution to maintain the strength of the patient, to counteract toxæmia, or to keep up the action of the kidneys.

2. **The Respiratory tract** is the next most important route.

(*a*) *The Nose.*—Drugs are administered by this route either for their local action in the nose or the lungs; or for reflexly stimulating the heart and respiration, or for systemic effect after absorption. Inhalation is carried on by the nose and the mouth. For local action we use collunaria, snuffs, bougies, paints, insufflations or sprays and nasal lavage. Sometimes drugs are sprayed into the nose for action after absorption, *e.g.*, the use of pituitary extract in the treatment of diabetes inspidus. (*See* pituitary).

(*b*) *The Larynx* is reached by inhalations, insufflations, sprays and pigments.

(*c*) *The Lungs.*—Through this channel vapours or atomised drugs rapidly enter the system. Ether, chloroform, and other gaseous anæsthetics are used to produce general anæsthesia after absorption from the lung surface; CO_2 is used to stimulate the respiratory centre; and various antiseptics are used in septic conditions of the lungs for their local effects. Lipiodol is introduced to visualise the condition of the lungs and the bronchioles under X-rays.

3. **The Skin.**—By the following methods, we can introduce medicaments into the body through the cutaneous surface:—

(*a*) *Enepidermic.*—In this method, drugs are simply kept in contact with the unbroken skin without friction or rubbing. Pastes, plasters, poultices, fomentations, pigments, creams, ointments, etc., are thus applied.

(*b*) *Epidermic, Iatroleptic or Inunction.*—In this method drugs are rubbed into the unbroken skin to promote their passage between the cells of the epidermis. For this purpose the drugs are either dissolved or mixed with oils or fatty substances. Familiar examples are the cod liver oil inunction in the treatment of rickets, and the use of blue ointment in the treatment of syphilis. This method is best suited for children, or for persons who cannot take oils by the mouth.

(*c*) *Cataphoresis* or *Ionic Medication.*—Drugs when in solution split up into their component molecules or ions. When a constant electric current is passed through them, the metallic ions and basic radicles are driven away from the positive pole, the acid radicles are driven away from the negative pole. This is utilised in medicine by soaking a thick pad in the solution of the drug to be used, attaching the negative pole of the pad when one desires to drive acid radicles to the tissues, the positive pole being on a neutral

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part. The exact opposite holds good when basic radicles have to be driven into the tissues.

(*d*) *Intradermal* or *intracutaneous* injection is the introduction of substances between the layers of the skin. This is done in certain skin tests, as the Schick test for diphtheria, or for the production of infiltration anæsthesia.

(*e*) *Inoculation.*—In this, the epidermis is punctured or scarified for introduction of medicaments; as vaccination.

4. **The Subcutaneous Tissues.**—These are reached by hypodermic injection, which is effected by a small syringe to which is attached a fine hollow needle. By this method the drug is quickly absorbed by the lymphatics and the blood-vessels, and any possible reaction in the stomach which may destroy its effect is avoided. Moreover one knows exactly the quantity of drug introduced into the system. It has however the disadvantage of forming abscess, which may be sterile from irritant drugs, or septic due to infection from faulty technique.

Hypodermoclysis is the introduction of large quantities of fluids into the subcutaneous tissue, as injection of saline or glucose.

5. **The Deep Tissues.**—By the same instrument drugs can be introduced into the deeper structures, *e.g.*, the muscles and nerves. When the injection is given into the muscles it is called *intramuscular injection*, and is generally given into the gluteal muscle. Intramuscular injections are given when the quantity to be injected is large, or when suspensions of insoluble drugs are used. Apart from the precautions necessary for all injections, the possibility of injecting the drug into a vein, or puncturing a nerve, should be kept in mind. Cases are on record where much harm has been done by injecting an irritant drug into a nerve. Familiar examples of intramuscular injections are those of calomel or bismuth in the treatment of syphilis.

6. **The Blood-vessels**—Through these channels, blood and saline fluid are *transfused*, and drugs are administered *intravenously*. It is the most rapid and certain way of bringing drugs into the circulation and tissues, and is generally used when a definite concentration of the drug is required very rapidly. Thus, during an emergency, when immediate action is necessary it is largely used, *e.g.*, intravenous injection of saline solution in the treatment of collapse of cholera; of strophanthin in cardiac failure; of glucose and insulin in diabetic coma. It is also used for certain drugs which are either decomposed in the digestive tract, or are too irritant to the stomach and subcutaneous tissues. Well known examples are the uses of antimony preparations in the treatment of kala-azar; neosalvarsan in the treatment of syphilis; and tryparsamide in the treatment of trypanosomiasis. The drugs used by this route must be

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in complete solution and must not react with the proteins of the blood. Unless there be definite indications, this route should be avoided. Injection of foreign substances directly into the blood alters the equilibrium of the colloids which in itself may cause alarming symptoms by producing flocculation shock.

7. **The Serous Cavities.**—These are only useful when the local action of the drug is required.

(*a*) *The Pleura.*—In empyema, we can wash out the pleural cavity with antiseptic lotions.

(*b*) *The Peritoneum.*—An injection of saline solution has been advocated in conditions of collapse. The peritoneum may be washed out with antiseptic fluids in some varieties of peritonitis.

(*c*) *The Tunica Vaginalis.*—Tincture or the weak solution of iodine, liquefied phenol or sodium morrhuate is sometimes injected to produce an adhesive inflammation in hydrocele.

8. **The Conjunctivæ and Lachrymal Ducts.**—Mydriatics, myotics, and drugs for local action on the conjunctivæ and lachrymal ducts are applied either as collyria, ointments, or powders.

9. **The Ear** is reached by injections, drops, insufflations, etc.

10. **The Bladder and Urethra** by injections and bougies.

11. **The Vagina and Uterus** by douches, injections, pigments, pessaries, medicated cottons, etc.

12. **Superior longitudinal sinus** is often punctured to introduce drugs in cases of infants when other veins are not accessible. This corresponds to intravenous injection.

13. **Intraspinal injection** through lumbar puncture is done for the treatment of cerebrospinal meningitis with antimeningococcal serum, for the production of spinal anæsthesia, or for the introduction of magnesium sulphate or antitetanic serum in the treatment of tetanus. Diffusible substances are readily absorbed from the subarachnoid space.

14. **Intraventricular injection** is done after trephining the skull in cases where the ventricles are to be reached. In infants under 18 months this can be reached through the anterior fontanelle.

15. **Intracardiac injection** is resorted to in case of sudden stoppage of an otherwise healthy heart. The best example is the intracardiac injection of adrenaline in collapse under anæsthesia, carbon monoxide poisoning, etc.

DOSAGE OR POSOLOGY

Having selected a drug and the route through which it is intended to be administered, the student should determine its dose. The word "dose" as ordinarily understood, means the quantity of a drug which is necessary to produce a certain

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pharmacological action either at once or after repetition. The study of these doses is called **posology**. By a *maximum dose* is understood the largest quantity which may be given to an adult without producing evil effects ; and by a *minimum dose*, the lowest quantity which is necessary to obtain a physiological action. The B.P. doses represent only average ordinary doses for an adult. The student should bear in mind that the action of a drug varies with different doses. Thus, tartarated antimony is a diaphoretic in $\frac{1}{32}$ to $\frac{1}{8}$ gr., and an emetic in $\frac{1}{2}$ to 1 gr. doses ; ipecacuanha powder is an expectorant in $\frac{1}{2}$ to 2 grs., and emetic in 15 to 30 grs. Though the B.P. posology is meant as a general guide, yet the practitioner can reduce the minimum and exceed the maximum limits of the pharmacopœial doses.

In determining doses, the following circumstances should be taken into consideration :—

1. **Age.**—The dosage varies considerably with the age. By *adult dose* is meant the dose for a person between 20 and 60 years of age. Children should get a fractional part of the adult dose. A practical method of calculating the children's doses under 12 years is given by Young. *The rule is to divide the age in years by the age in years plus* 12 ; *the resulting quotient is the proper fraction of an adult dose.* Thus the dose

for a child of 1 year, will be $\frac{1}{1+12}=\frac{1}{13}$ of an adult dose

„ 4 years „ $\frac{4}{4+12}=\frac{1}{4}$ „

Cowling's Rule.—Adult dose $\times \frac{\text{age next birth day}}{24}$

The dose for a child of three years old will be $\frac{4}{24}$ or $\frac{1}{6}$ of adult dose.

Dilling's formula is $\frac{\text{age}}{20}$ when calculating with metric weights.

From 12 to 16 years, $\frac{1}{2}$ to $\frac{2}{3}$, and from 17 to 20, $\frac{2}{3}$ to $\frac{4}{5}$, are the proportions. Over 60 years, the dosage should again be diminished slightly. For hypodermic medication, the dose is one-half of what is given by the mouth, and for rectal medication, it is the normal dose plus one-fourth, except in the case of strychnine, which should be exhibited in smaller quantities than when given by the mouth.

2. **Sex.**—Women, as a rule being more delicate than men, cannot bear full adult doses. The menstrual period should also be taken into consideration. For instance quinine, if given during the period, may cause alarming hæmorrhage.

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3. **Size and Body Weight.**—The quantity which is required to produce a certain physiological effect in a strong, healthy, and stout person of more than average size and weight, is certainly not necessary to produce the same action on a thin and weak individual.

4. **Temperament** has some influence on doses. A person with a sanguine or nervous temperament requires smaller doses than one with a lymphatic one.

5. **Idiosyncrasy.**—Individual susceptibility to the action of a particular drug or drugs has long been recognised. We often come across a patient who cannot take a grain of potassium iodide without coryza, though ordinarily many can take it in larger doses without inconvenience. Quinine sulphate does not agree with many. Others again are readily salivated by quite small doses of mercury.

6. **Toleration and Habit.**—Certain drugs, fail to produce the same effects with the same dose, when continued for a lengthened period. This is what specially happens with opium. Its dose must be increased after a while in order to get the full or the original effects of the drug. This gradual loss of activity is due to **toleration by custom.** Sometimes the person taking it becomes so addicted to its use that he actually craves for and indulges in it, to the detriment of his health. This craving for a particular drug is called a **habit.** Like opium-habit, persons may contract alcohol-habit and cocaine-habit. Tolerance is also established in the case of arsenic, as the arsenic-eaters of Styria. (*See* Arsenic).

7. **Rate of Absorption and Excretion.**—The quicker the absorption, or the slower the excretion, the greater is the effect produced by a drug. Thus morphine, subcutaneously injected, requires a smaller dose to produce a definite action, within a definite period, than what is necessary if administered by the mouth or rectum.

8. **Mental Condition.**—A morbid inclination of the mind towards the action of a particular drug increases the action of the same. Thus, if a patient can be convinced that he will sleep by a certain draught, a small dose of a hypnotic may induce sleep.

9. **Fasting.**—A drug acts more powerfully on an empty stomach than on a full one. Thus the same quantity of alcohol which would intoxicate a person if taken on an empty stomach, can be ingested with impunity if taken during or after meals.

10. **Disease.**—Many diseases considerably modify the dosage of medicines. Thus, opium is borne in surprisingly large doses in biliary and renal colics. Large doses of mercury are tolerated in syphilis.

11. **Climate.**—It is a well-known fact that alcohol can be consumed in larger quantites in cold countries than in hot climates.

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12. **Time of Administration.**—Vital force is lowest at the early hours of the morning. Consequently, in debilitating diseases, simulants are more necessary at this time than later on in the day. It is useless to administer even a very large dose of chloral hydrate when the person is in active labour; it should be given at bedtime. Cod-liver oil should always be given after food; given at any other time it may derange digestion. Iron and arsenic should always be given on a full stomach.

13. **Preparations of a Drug.**—Alkaloids, glycosides, neutral principles, extracts, etc., are all prescribed in smaller doses than the crude drugs from which they are prepared. Thus, for 2 grs. of emetine, we should have to prescribe about 25 grs. of ipecacuanha powder.

14. **Accumulation.**—Ordinarily a drug after introduction into the body is either slowly or rapidly excreted. But if we continue to administer it very frequently for a sufficient length of time, *i.e.*, so quickly that it cannot be fully eliminated, a time may come when it will accumulate to such an extent as to produce suddenly toxic symptoms. This is called the *cumulative action* of a drug. It may be caused by the following circumstances:—

(*a*) *Rapid absorption and slow elimination of a drug.*—This occurs in the case of lead and mercury, both of which are eliminated slowly and with difficulty, by the kidneys.

(*b*) *Slow excretion due to fixation of the drug in the tissues.*—Digitalis is cited as an example of this class. During a course of digitalis treatment, if no precaution is taken, symptoms of poisoning may suddenly develop, without any increase of the dose.

(*c*) *Sudden solution and absorption of a sparingly soluble drug owing to some changes in the contents of the intestine.*

ANTAGONISM AND SYNERGISM

By antagonism is meant the weakening or prevention of the action of a drug by that of another. An antagonist may be a drug, or a substance formed in the body. They may act by (1) *Distoxication*, *i.e.*, by chemical combination with one another, *e.g.*, free acids and alkaline carbonates, oxalates and lime salts; (2) *True antagonism.* Here the drugs have no chemical affinities for, nor do they react with, each other, but produce opposite effects by acting either on (*a*) *the same structures*, as bromides and strychnine on the spinal cord; or (*b*) *different structures, e.g.*, adrenaline and amyl nitrite; the former constricts the vessels by stimulating the nerve-endings, while the latter dilates the vessels by direct action on the muscles.

Just as the weakening or prevention of the action of one drug by that of another is known as antagonism, the

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one-sided or reciprocal augmentation of such action is known as *synergism* or *potentiation*. For example magnesium sulphate and sulphuric acid make a stronger purgative than magnesium sulphate given alone. It has been found that doses of cocaine which by themselves produce no appreciable effects, very markedly increase the effects of adrenaline on the vessels, the dilator of the iris, etc. Bromide and chloral hydrate make a better hypnotic than either used alone.

INCOMPATIBILITY

A prescription should not contain such ingredients which can counteract one another either physically, or physiologically, when mixed together. If they do so, they are known as **incompatibles**.

Incompatibility, therefore, may be of the following kinds :—

I. **Physical.**—This is also known as *pharmaceutical*, and occurs when the ingredients are not soluble in water, so as to produce a clear solution. As oils, insoluble powders, some spirits, resinous tinctures, some extracts, etc., when ordered in a mixture.

II. **Chemical.**—Such drugs should not be prescribed as would chemically react on one another, unless such a reaction is desired. Chemical incompatibility can be classified under two heads :—

A. *Homogeneous.*—In this *no visible change of form*, such as the liberation of a gas or formation of a precipitate occurs, though the colour may be changed. Thus, acids and bases are chemically and physiologically incompatible with each other ; *e.g.*, lactic acid with lime water, diluted hydrochloric acid with aromatic spirit of ammonia. Again, if the resulting salt is soluble and poisonous, the chemical neutralisation cannot resist the toxic action, as hydrocyanic acid and alkalies, for KCN is as poisonous as HCN, although the alkaline carbonates are not incompatible with HCN.

B. *Heterogeneous.*—In this there is *a visible change of form*, *i.e.*, the production of a gas or a precipitate ; CO_2 is the chief gas liberated in such a decomposition, sometimes H_2S. The precipitates or the insoluble compounds form the largest chemical incompatibles. This class can again be subdivided into :—

1. *Intentional.*—Seidlitz powder, black wash, all effervescing mixtures, etc., are examples of this variety. Vegetable astringents with chalybeates, and lead salts with solutions of opium also come under this category.

Unless the incompatibility in the prescription is intentional the dispenser should first consider whether the incompatibility is of such a nature as would endanger the

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life of the patient, when it should be referred to the prescriber; if it is not of such a nature the prescription should be dispensed as ordered adopting such method as will give as satisfactory a combination as can be expected under the circumstances.

2. *Avoidable.*—This form of chemical incompatibility is very difficult to master. A complete knowledge of chemistry and solubility of drugs can only help the student out of this difficulty. The following rule would greatly minimise his errors;—"*A drug should never be ordered in combination with any of its tests or antidotes.*" Thus, carbonates should not be given with free acids (except HCN); acid salts, basic salts, double citrates, *e.g.*, scale preparations of iron, halogens, with solution of ammonia, etc.

Alkaloidal salts, with the exception of quinine sulphate, quinine tannate, quinidine sulphate, physostigmine salicylate, ergotoxine ethanesulphonate, emetine and bismuth iodide, and pelletierine tannate, are soluble in water, although the free alkaloids are only sparingly soluble. Therefore alkaloidal salts should not be prescribed with alkaline carbonates or hydroxides, *e.g.*, liquor strychnine with aromatic spirit of ammonia, morphine salts with bicarbonates of sodium or potassium, as free alkaloids will be precipitated. Potassium iodide and tannic acid also throw down alkaloidal precipitates, specially if the solution is concentrated. Many fatal accidents have taken place from swallowing the last dose of a mixture containing a poisonous alkaloidal precipitate. Although, to some extent, the alkaloidal incompatibility can be avoided by the addition of HCl and alcohol yet it is a safer plan to follow the following practical rule, viz. "*All poisonous alkaloids as far as possible should be prescribed in simple solution, and not in too concentrated a state.*"

Sometimes explosive combinations result from inattention to grave incompatibility (*see* below).

III. **Physiological.**—When the pharmacological action of a drug is antagonised by that of another, both drugs are *physiological incompatibles* or *antagonists*. It is presumed that this antagonism takes place either in the blood or in the tissues. We do not know any drug which can fully and completely counteract the action of another on all points, though instances are common where *partial antagonism* takes place. Thus, opium contracts the pupils and depresses the respiratory centre, belladonna dilates the pupils and stimulates the respiratory centre (*see* Opium and Belladonna); hence both of them are partially physiological incompatibles to each other. Digitalis counteracts the action of aconitine on the heart; and strychnine and brucine that of bromides and chloral hydrate on the cord. The depressant action of aconitine on the heart is also neutralised by the stimulant action of atropine. Pilocarpine increases, while

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atropine decreases, both salivation and perspiration. (*see* Antagonism, page 50).

EXPLOSIVE COMBINATIONS

Certain drugs, such as chlorates, bichromates, iodates, nitrates, picrates, permanganates, oxide of silver, etc., are rich in *oxygen* or part with it very easily; while others, such as sulphur, sulphides, iodine, reduced iron, hypophosphites, organic powders, charcoal, camphor, iodide of iron, ammonia salts, essential oils, etc., are *easily oxidisable.* An admixture between any two of these classes is sure to result in an explosive combination. The following are a few typical examples:—

1. A few tablets of potassium chlorate kept in a pocket with a box of safety matches caused explosion.
2. Potassium chlorate with tannic acid, catechu, morphine hydrochloride, or gallic acid mixed as a dry powder has been known to explode.
3. A mixture of liquor ferri perchloridi, glycerin and potassium chlorate explodes when warm.
4. Calcium hypophosphite alone, when triturated hard, sometimes causes explosion. Never heat it with glycerin.
5. Potassium permanganate should not be made into a pill with vegetable extracts or combined with glycerin.
6. Oil of turpentine and sulphuric acid, and amber oil and nitric acid are sure to explode violently.
7. Oxide or nitrate of silver with creosote forms a compound which may take fire if it becomes warm.
8. Chromic acid with glycerin, ether, strong alcohol, or organic substances causes an explosive combination.
9. Chloral hydrate and spt. ammon. aromat. in a mixture may liberate so much chloroform as to explode.
10. Bismuth subnitrate and sodium bicarbonate given in a mixture liberate CO_2, and may cause an explosion if the bottle is corked before allowing the gas to escape.
11. Tr. iodine and solution of ammonia should not be prescribed together as iodide of nitrogen is formed, which causes explosion.
12. Erythrol tetranitrate is very sensitive to percussion. A young chemist lost his life from explosion due to the rubbing of the tetranitrate with milk-sugar in a mortar.
13. Chloride of lime triturated with sulphur causes explosion.

POISONOUS COMBINATIONS

1. Potassium chlorate and potassium iodide in solution do not react in ordinary temperatures but in the body produce a poisonous product, probably iodate of potassium.
2. Potassium chlorate given with syrup of ferrous iodide liberates free iodine in the stomach and causes severe gastric irritation.
3. Hydrocyanic acid dilute with metallic hydrates, carbonates, subnitrates, or subchlorides forms cyanides of metals which are more poisonous than the acid.

COMBINATION OF DRUGS

The main object of the prescriber should be to present his patient with an effective and rational prescription free from incompatibles. An admixture of several ill-understood and

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ill-chosen drugs, can no longer be tolerated in these days of rational therapeutics. No drug should be ordered unless the prescriber is sure of the pharmacology of the drugs he is using. Simplicity in combination should be the rule, but it does not follow that one drug only is to be prescribed at a time. An effective combination of judiciously selected drugs is of great value in the treatment of disease. The following are the advantages of a good combination :—

1. *By a combination of various drugs, whose actions bear resemblance with one another, we can augment or intensify certain properties of a drug.*—Thus, a mixture of chloral hydrate and potassium bromide makes a better hypnotic than either given in large doses. (*see* Synergism, page 51).

2. *By a careful admixture of corrigens, we can correct unpleasant and undesirable properties of a drug.*—Thus, ginger is added to Pulv. Rhei Co., Pulv. Jalap. Co., to remove griping. Hydrobromic acid lessens cinchonism.

3. *By a combination of two or more drugs, individually producing entirely different physiological effects, we can sometimes increase the potency of a remedy in a particular direction.* —Thus, by combining mercury with digitalis and squill, we can increase the diuretic properties of the latter drugs.

4. *By mixing such drugs as chemically decompose each other we at times get better results from the resulting products.* —Thus by giving potassium or sodium bicarbonate with citric acid, we get the benefit of carbonic acid gas and potassium or sodium citrate.

5. *By a combination of such substances as would assist the solubility or absorption of a drug, a more effective remedy can be obtained.*—Thus, salicylic acid is almost insoluble in water, but it is rendered entirely soluble by the addition of borax, alkaline carbonates, hydroxides, etc. The absorption by the skin of the alkaloids of belladonna is greatly facilitated if belladonna is combined with fat, glycerin, oil, or chloroform.

ART OF PRESCRIBING

WEIGHTS AND MEASURES IN A PRESCRIPTION

The weights and measures of capacity and length to be used in a prescription are those of the Metric System (*see* p. 11). The Imperial system however is still used, and also the scruple, though rarely. Besides, certain signs indicating weights and measures of capacity are also common, which have not been officially recognised. They are :—

Gr. = Granum, 1 grain = $\frac{1}{480}$ of a Troy ounce, or $\frac{1}{437}$ of an Avoirdupois ounce.

℈ = Scrupulum, 1 scruple = 20 grains.

℥ = Drachma, 1 drachm = 3 scruples or 60 grains or $\frac{1}{8}$ of a *fluid* ounce, or 60 minims.

℥ = Uncia, 1 ounce = 1 Troy ounce (480 grs.) or 1 fl. oz. (480 minims) or 437.5 grains of water.

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M. = Minimum, 1 minim = $\frac{1}{60}$ part of a drachm or the volume of 0.91145 grain of water.
Gtt. = Gutta, 1 drop, supposed erroneously to represent 1 minim.
O. = Octarius, 1 pint = 20 fluid ounces, or 1¼ lbs. of water.
C. = Congius, 1 gallon = 8 pints or 10 lbs. water.

As these symbols are apt to be misleading, the B.P. recommends that prescribers should cease to employ them. Solids should be prescribed in grains (gr.), when Imperial system is used, and ounces (oz. = 437.5 grs.); and liquids in minims (m.) and fluid ounces (fl. oz.). The quantities should be written in Arabic numerals. The symbol of gramme should be G. and for grain (gr.)

When 'drop' is used it should be measured by means of a tube which delivers in 20 drops 1 G. of distilled water at 15° C.

English Domestic Measures

A tea-spoonful = 1 fluid drachm, or a little more.
A dessert-spoonful = 2 fluid drachms (about).
A table-spoonful = 4 fluid drachms or ½ ounce (about).
A wine glassful = 2 fluid ounces, or more.
A gill = 4 fluid ounces, or more.
A tea-cupful = 7 fluid ounces or more.
A breakfast-cupful = 8 fluid ounces or more.
A glassful = 12 fluid ounces or more.
A tumblerful = 15 to 20 fluid ounces.

These are only average measurements, for no cups or spoons are of the same size.

Indian Domestic Measures

MEASURES OF CAPACITY CURRENT IN THE BENGAL PRESIDENCY

A Half-kancha = ⅛ chattack or $\frac{1}{128}$ seer = 2 fl. drachms (about).
A Kancha = ¼ ch. or $\frac{1}{64}$ seer = 4 fl. drachms, or 218.75 grs. of distilled water.
A Half-chattack = ⅛ poa or $\frac{1}{32}$ seer = 1 fl. ounce (about).
A Chattack = ¼ poa or $\frac{1}{16}$ seer = 2 fl. ounces (about).
A Poa = ¼ seer = 8 fl. ounces (about).
A Half-seer = ½ seer = 16 fl. ounces (about).
A Seer or 64 kancha, or 16 chattacks = 32 fl. ounces (about),

MEASURES OF CAPACITY CURRENT IN THE BOMBAY PRESIDENCY

A Sundia-palliful = 1 drm.
A Curd-palliful = 5 tollas or 2 ounces,
A Swayapak-palliful = 10 tollas or 8 ounces.
A Panchpatriful = 8 or 12 ounces.
A lota or tambiaful = 3 or 4 lbs.

Indian Domestic Weights

1 Rupee or 1 tola	=	180 grains
½ „ ½ „	=	90 „
¼ „ ¼ „	=	45 „
1 Nickel 2 anna	=	90 „
1 „ anna	=	60 „

PRESCRIPTION WRITING

A prescription is simple, when it contains a basis and a vehicle or excipient with or without a corrective; and complex when it contains several adjuvants and corrigents besides the basis. The construction of a model prescription should be in the following order :—

1. The superscription, which consists of the symbol Re. which

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originally symbolized the planet Jupiter, but now stands for *recipe* or take thou.

2. The **inscription**, or the body of a prescription, consisting of the names and quantity of drugs ordered, and contains the *basis*, or the chief ingredient; the *adjuvant*, to assist the action of the basis; the *corrigent*, to correct the injurious effects of other ingredients; and the *vehicle* or *excipient*, to give the prescription a suitable form.

3. The **subscription**, or the directions to the dispenser, such as *misce, fiat, mist., pilula, etc.*

4. The **signature** (from L. *Signature*—let it be labelled) or the directions to the patient. This is written either in English or in vernacular.

5. The **Prescriber's name or initial** and the **date**. These are put at the bottom. The patient's name should be written at the top of the *recipe*.

The following is an example

Patient's name :—

Superscription : Re

Inscription :	Quininæ Sulphas,	gr. 10 *(basis)*
	Acid. Hydrobrom. dil.,	m. 10 *(adjuvant)*
	Syrup. Limonis,	ms. 60 *(corrigent).*
	Aqua Chloroformi,	ad fl. oz. 1 *(vehicle)*

Subscription : Fiat mistura, Misce
Mitte talis six

Signature : Two table-spoonfuls thrice a day

Date : *Prescriber's Name :*

It will be observed that quinine is given with the object of checking malaria, and as the sulphate is insoluble in water, Acid. Hydrobromic. Dil. is used to dissolve it, and also to prevent cinchonism. Chloroform water is used as a diluent and to make the dose a measurable quantity. A vehicle may be of no medicinal value, *e.g.*, plain water, or only used to give flavour. Sometimes it has a medicinal value, as when infusions are used. "ad" fl.oz. 1 means that after all the ingredients have been measured the vehicle should be added to make the total quantity one ounce.

In the above prescription the quantities have been given for a single dose, and the dispenser is asked to supply six doses. Sometimes, however, instead of depending on the dispenser to calculate the total quantities of each ingredient, the physician makes the mental calculation for the whole amount contained in the prescription.

The prescription in this case takes the following form :—

Patient's name.—

Superscription : Re

Inscription :	Quinin. Sulphas	gr. 60 *(Basis)*
	Acid. Hydrobrom. Dil.	ms. 60 *(Adjuvant)*
	Syrup. Limonis	ms. 360 *(Corrigent)*
	Aqua Chloroformi	ad. fl. oz. 6 *(Vehicle)*

Subscription : Fiat mistura, Misce
Put six marks

Signature : One mark three times a day

Date : *Prescriber's name :*

Every prescription should be written with a definite object. The prescriber therefore should weigh each drug carefully before writing.

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Let us take another example. Supposing we wish to write a sleeping draught for an adult, we first of all think what hypnotic will suit our patient, and decide on chloral hydrate and write accordingly

℞
Chloral Hydras, which forms the *basis*

Then we argue that another preparation like potassium bromide will help in its action and will act as an *adjuvant*, we therefore write as

℞
Chloral Hydras
Potassii Bromidum

We now consider an agreeable corrective and vehicle which would give it a flavour, and therefore add further

Syrupus Aurantii
Aqua Anethi Dest.

Having written so far we consider the dose. Here we must be guided by the object for which the prescription is given, and whether the patient should take only one dose or more than one. We order for two doses in case the first dose does not produce the desired effect. The dose of chloral hydrate is 5 to 20 grs., and of potassium bromide is 5 to 30 grs. We make a mental calculation and decide on giving 15 grs. of each, and for two doses we order grs. 30 of each. Now we add 60 ms. of syrup for each dose and sufficient vehicle to make up the total bulk to 2 ozs. Then we proceed to write directions to the dispenser, *i.e.*, to mix and make a draught, *viz.*—M. ft. Haust., and the final direction—*Sig.* one ounce at bed time to be repeated after two hours if necessary.

The complete prescription will now take the following form :—

Patients name :—

Re

Chloral Hydras Pot. Bromide	...	a a grs. 30
Syr. Aurantii	...	ms. 120
Aqua Anethi Dest.	...	ad. fl. oz. 2

M. ft. Haust.

Sig.—One ounce at bed time to be repeated if necessary after two hours.

Date : · *Prescriber's name* :

In writing prescriptions the following points should be observed :—

1. Always begin each line with a capital letter.
2. It is better to write the names of the active ingredients first and then of corrective, etc., and vehicle or excipient last.
3. Use Latin names for the ingredients and for the directions to the dispenser. The directions to the patient may be given in commonly used Latin ; but the dispenser must write the directions on the label either in English or in the vernacular of the place.
4. When in doubt always write in plain English. It is most important that the dispenser should understand the meaning of expressions used in the prescription.
5. Never hand over the prescription without reading it over again.

ELEGANT PRESCRIPTIONS

Elegance in a prescription should always be aimed at, but it does not follow that the student should prescribe only fancy pills, capsules, tablets and cachets. These are good and useful, but they cannot supply the place of a mixture. The importance of

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giving a mixture in an inviting and palatable form cannot be overestimated. We have various flavouring agents. Aromatic syrup, syrups of orange, glucose, lemon, Virginian prune, tolu and ginger are the popular ones. During the hot months, mixtures containing syrups soon decompose, but glycerin and flavouring waters may be substituted for them. Spirit of chloroform, chloroform water and liquid extract of liquorice cover the taste of many bitter and saline mixtures. Syrup of yerba santa disguises fairly well the taste of quinine salts. Rose water, orange-flower water, cinnamon water and anise water are good flavouring vehicles either for mixtures or for lotions. Cinnamon water disguises the odour of castor oil. Syrups of rose and red poppy are only used as colouring agents. Compound tinctures of lavender and cardamoms are used both for flavouring and for colouring purposes. Liniments or ointments can be perfumed by otto of roses, oil of neroli and lavender. Nauseous and bitter powders can be given in cachets or pills, which can be coated or gilded.

DIRECTIONS TO THE PATIENT

Make it a point to give directions in a definite manner. They should be short, simple and to the point. It is very important to mention the hour of the day when medicines are to be administered. To the student this may appear confusing in the beginning, but the following hints will aid him in this direction :—

1. Mineral acids, as a rule, are given after meals.
2. Alkalies when used to neutralise acid secretion should be given after food, and when prescribed as a systemic alkaliser should be given between meals.
3. Gastric sedatives, such as dilute hydrocyanic acid, bismuth salts, are best given on empty stomach, as we want their local action.
4. Pepsin, papain, taka-diastase should be given immediately after or along with meals.
5. Dilute hydrochloric acid when prescribed to help intestinal digestion should be given one to two hours after food, so also pancreatin and other pancreatic ferments.
6. Cod-liver oil and its preparations should be administered after and not before food. If given before they spoil the appetite.
7. All preparations of iron, specially the astringent varieties, are to be administered after meals.
8. All stomachics and bitter tonics, such as calumba, chiretta, quassia, are given quarter to half an hour before food.
9. Arsenic is always given after meals, except in a few rare cases, when its local action on the stomach is desired.
10. Potassium permanganate is always given after food.
11. Purgatives should be given either at bed time or early in the morning depending upon the rapidity of their action. Castor oil and salines are best given early in the morning as they take only a few hours to act. The more slowly acting ones, e.g., bed pills containing aloes. etc., should be given before retiring at night.
12. Emmenagogues should be taken at least one week before menstruation.
13. All diaphoretics act well when the patient is kept warm, and diuretics when cool.
14. Hypnotics, as a rule, should be taken at least half an hour before going to bed; but sulphonal two or three hours before, as it dissolves slowly.
15. Morphine should be administered subcutaneously when the patient is in bed.
16. Bromides, when given as a sedative, are to be administered after meals or at bedtime.

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PRESCRIPTION FOR CHILDREN

Great tact and caution are required in prescribing for children. The hints given below will greatly help the student in this direction :—

1. The dosage must be in proportion to the age.
2. The bulk of a mixture must be small, not exceeding one or at the most two tea-spoonfuls.
3. Medicines must be made as palatable as possible. Children like either sweet or tasteless medicines. They refuse bitters. Quinine ethyl carbonate (euquinine) or aristochin may be used as tasteless substitutes for quinine salts. Quinine should not be dissolved in mineral acids, as its bitterness is intensified.
4. Infants do not refuse either castor oil or cod-liver oil, but older children often reject the former. Cod-liver oil with extract of malt is never refused.
5. Do not order pills for children, give dry drugs in the form of powders mixed with honey, syrup, milk, sweetened water, malt extract, or jam.
6. Children bear belladonna and hyoscyamus in fairly large doses.
7. Arsenic, too, is well borne, some choreic children can take very large doses without harm.
8. A tea-spoonful of castor oil to a new-born babe is not a big dose.
9. Children are *very susceptible to opium.* Opium and its preparations should therefore be used with caution in children's practice*.
10. Plain dill or anise waters make good all-round general vehicles for children's mixtures.
11. For round worm, santonin must be given on an empty stomach at night and then followed by a dose of Gregory's powder next morning. It is best given with calomel and sugar followed by a saline if necessary.
12. Children tolerate calomel better than adults and are rarely salivated.
13. Expectorants are best given in the form of syrups or mixed with a syrup.

*In some parts of India infants are habituated to the use of opium. It is given with a view to keep them quiet while their mothers are at work. Many wet-nurses secretly administer it to their wards. The writer has seen an infant only 14 months old taking daily one grain of opium, without any other evil effects than constipation.

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PART III

PHARMACOLOGY AND THERAPEUTICS

HOW DRUGS ACT

By the action of a drug on the human organism is understood the interaction between a drug and the blood and the tissues, whereby either the existing functions are altered, or certain functions are brought more into prominence which were latent before. Thus, the functions may be increased or diminished, and the drug is then said to *stimulate* or *depress* as the case may be. Sometimes this stimulation has an injurious effect on the tissues and it is then known as *irritation*. A moderate degree of stimulation continued for a long time leads to fatigue or exhaustion of the organs concerned.

Some drugs act more powerfully on certain organs and tissues than others, and this preferential effect is known as the *selective action of the drug*. This fact has been taken advantage of in the modern treatment of parasitic diseases and forms the basis of chemotherapy. Substances have been discovered which are supposed to be harmful to the infecting parasites, *i. e., parasitotropic*, and at the same time harmless to the host, *i.e., not organotropic*. The conception of chemotherapy is, however at its best, a speculation, and most of the parasitotropic agents act not so much by their selective affinity for the parasite but by definite pharmacological action on the cells of the body of the host. *(See* Chemotherapy, page 2).

A drug may affect the body *directly, i.e.,* when it comes in contact with a particular organ and produces its effects on that organ. The direct action of cantharidin on the skin is irritation. This action is also known as the *local action*. Many drugs, after absorption produce changes on other organs of the body and this action is then known as the *systemic effect*. The action of digitalis on the circulation or kidneys is the systemic effect of the drug after absorption. This is also called *indirect* or *remote action* of the drug. Thus the immediate local action of aconite on the tongue is tingling and numbness, and its indirect or remote action on the heart is slowing of beat due to stimulation of the vagal centre.

By *primary action* is meant the effect that a drug produces in its unaltered state When a drug forms a different compound in the body which produces the physiological effects, it is known as the *secondary action* of the drug. Hexamine when

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excreted with the urine acts as an antiseptic by being converted into formaldehyde.

It is not always very easy to explain exactly how the different drugs produce their pharmacological effects on the system. Although many attempts have been made to explain how the different drugs produce their effects, still we are far from any satisfactory solution as to the real nature of the action of most of them. Since the processes of life are governed by the chemical and physical changes in the constituents of the cells, it is possible that the different drugs may act by altering or modifying these chemical and physical factors in the cells by entering into definite chemical combination with the constituents of the protoplasm and produce corresponding changes in their function. An attempt was therefore made to explain the action as being due to *chemical changes*. Although the effects produced by some drugs are due to these changes, yet the action of many is produced differently and cannot be explained by chemical theory alone. It will be seen, when discussing drugs acting on the autonomic nervous system, that drugs while stimulating the different nerve endings act by liberating chemical substances which transform a nervous stimulus into a chemical reaction; for instance, stimulation of parasympathetic acts by production of *acetyl choline* and that of sympathetic by the formation of *adrenaline-like* substance. Some drugs act in a purely *mechanical* way, while others affect the various cells of the body by altering the *surface tension* resulting in osmosis, and modify the particular function of the cells. Mayer and Overton explain the action of another group of drugs, *viz.* the narcotics, as being due to their solubility in lipoids. They argue that in order that a drug may produce any physiological effect it must first get into the cell, and other things being equal, one would expect a quicker and more powerful effect from a lipoid soluble substance than from one that is not thus soluble. While discussing narcotics it will be seen that there are many objections to this theory, and that the action of all narcotics cannot be explained on the theory of lipoid solubility. Yet another school holds that it is not the solubility of a particular drug in the cell that determines the action, but the activity depends upon the adsorptive power owing to the colloidal nature of the cell protoplasm. This is how the bactericidal action of mercury (*see* Mercury), and adsorption of toxins by kaolin are explained.

The Chemical Composition and Constitution and the Physiological Action of a Drug

Recent works have demonstrated that the physiological action of a drug very often depends upon its chemical constitution as will be evident from the following:—

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(*a*) *The molecular arrangement in a compound sometimes determines the action of a drug.* Thus isomerides have the same chemical composition and the same percentage of weight, but differ in properties, on account of their different molecular arrangements. Resorcin and pyrocatechin are isomers $C_6H_4(OH)_2$. The former is sweet, the latter is bitter.

(*b*) *It is possible to modify the physiological action of a drug by artificially modifying its chemical constitution.* Fraser, Crum Brown and others have shown that by introducing a *methyl radical* into the molecules of strychnine, brucine and thebaine, new compounds are formed, which instead of acting as convulsants, are paralysers of the peripheral terminations of the motor nerves.

Similarly benzol, C_6H_6, the mother substance of the coal-tar series, has a low toxicity, because it cannot react with protoplasm. It becomes toxic by replacing part of the H atoms by other groups, especially by OH (forming phenols) or by CO_2H, or by both. The OH radicle is the most active, the antiseptic and toxic actions increasing with the number of OH groups. Thus: benzol = C_6H_6; phenol = C_6H_5OH; resorcin = $C_6H_4(OH)_2$. The introduction of CO_2H group alone *i.e.*, benzoic acid $C_6H_5(CO_2H)$ does not render the substance more active. But both OH and CO_2H, *i.e.*, salicylic acid, $C_6H_4 \begin{matrix} OH \\ CO_2H \end{matrix}$ results in a compound which is less toxic and less antiseptic than phenol, but has a peculiar anti-rheumatic property. The substitution of an H of the C_6H_5 in phenols by *alkyls* = Cresol, $C_6H_4 \begin{matrix} OH \\ CH_3 \end{matrix}$ leads to an increase of the antiseptic power, and diminishes at the same time the toxicity to tissues.

The Action of a Drug and its Power of Dissociation into Ions

When we consider the action of a powerful drug like strychnine, we find that its various salts produce the same effect which the acid radicle (sulphate, nitrate, etc.) does not modify. This is not however the case with less powerful bodies, *e.g.*, sodium; here the acid radicle with which it is combined greatly modifies its action, as is observed in the different effects resulting from the administration of NaCl and Na_2SO_4. To appreciate these differences of action it is essential to understand the *ionic theory.* All substances are divided into two groups, *electrolytes* and *non-electrolytes.* An electrolyte is a substance which is capable of being decomposed by the electric current, as sodium chloride, potassium bromide, etc. The theory assumes that certain substances such as inorganic acids, salts and bases in

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solutions undergo partial decomposition into their constituent elements or radicles called *ions*. These ions carry definite charges of electricity. Thus, sodium chloride, if dissolved in water, exists in part commingled, but not chemically bound sodium *kations* and chlorine *anions*.

NaCl	=	Na	+	Cl
(Electrolyte)		+ ion		− ion
		or kation		or anion

A non-electrolyte is a substance which cannot be further decomposed without losing its chemical identity. In ionic dissociation when the solvent is evaporated the salt is obtained in the same state as before solution, in chemical decomposition however the evaporation of the solvent will not re-unite the separate ingredients.

The importance of this theory to pharmacology is that it is the ions of the salts and not the whole molecule which give rise to pharmacological action. For instance, when an ionisable substance is introduced into the blood it has a threefold effect on the functions of the body, *viz.*—

(*a*) That due to the influence of its kation,

(*b*) that due to the influence of its anion, and

(*c*) pure salt action.

Sometimes the basic and sometimes the acid ion produces the chief effect, and when neither ions are potent we get the typical salt action. When the two ions are of approximately the same potency we have the combined effects of both ions. The following examples will serve to illustrate :—

NaCl=typical salt action.

Na_2SO_4=action of acid ion predominates, and acts as a purgative.

$FeSO_4$=astringent and hæmatinic, action of basic ion predominates.

$MgSO_4$=action of both ions predominates, therefore although the sulphate ion is common with $NaSO_4$, it acts as a more powerful purgative because of the Mg-ion.

Drugs that are not dissociated in the tissues act as molecules and not as ions. This important factor should be remembered to avoid confusion. Thus potassium cyanide is a poison because CN-ion is dissociable, while in potassium ferrocyanide the CN-ion is not dissociable and therefore this salt is not a poison. Again inorganic arsenic compounds are poisonous, whereas cacodylic acid has not the same toxicity because it does not ionise.

It follows therefore that the action of certain drugs depends not only on the amount of dissociation which they undergo but also on the relative absorptive power of the dissociated ions. Scale preparations of iron which do not dissociate are not astringents and do not impair digestion. Mg-ion being absorbed with difficulty and excreted rapidly, its effects are not observed when administered by the

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mouth, although given parenterally it has a profound depressing effect on the central nervous system. The disinfecting power of mercurials varies with the amount of dissociation which the different salts undergo and not on the quantity of mercury in solution. Finally, potassium salts given by the mouth produce no toxic effect because their rate of excretion exceeds that of absorption.

The Reaction of Body Tissues and Body Fluids and the Action of Drugs

By the term reaction of a solution is meant the degree of acidity and alkalinity. The acidity and alkalinity of tissues depend upon the dissociation of H and OH ions, and the degree of acidity of any solution depends upon the relative amounts of free hydrogen ions (H) and free hydroxyl ions (OH) which it contains. When both ions are balanced the solution is neutral. These two ions part readily with their electric charges and produce marked alterations in the functions of cells. Chemically pure water is neutral and when it dissociates it yields equal amounts of H and OH ions. At 22°C. 10,000,000 litres of pure water contains 1 gm. of H and 1 gm. of OH ions. The concentration of hydrogen ions (cH) is therefore 10^{-7}, and the concentration of hydroxyl ions (cOH) is 10^{-7}.

Such negative figures are difficult to deal with in practice, and therefore the potential of H-ion concentration is taken as the standard, rather than the actual H-ion concentration itself. The hydrogen-ion-concentration-potential or *p*H is the decimal logarithm of the reciprocal of cH, and in the case of water, *p*H = 7.0, and a standard of *p*H = 7 may be taken as neutral.

The tissues and fluids of the body are normally neutral, inclining a trifle towards alkalinity, *i.e.*, *p*H=about 7.1 to 7.8. The *p*H of gastric juice is 0.9 to 1.6 ; urine, 6.0 ; cow's milk, 6.7 ; human milk, 7.1 ; saliva, 6.9 ; pancreatic juice, 8.3 ; etc. Living cells are dependent upon the maintenance of a strictly limited H-ion concentration in their environment for the normal performance of their functions.

The normal blood has a *p*H range of from 7.3 to 7.5 ; and life is incompatible when the *p*H of blood is below 7.0 or above 7.8. While the *p*H of different excretions varies between wide limits, the maintenance of the *p*H at its normal level in the blood and tissues is very important. This is regulated by a fine adjustment of different mechanisms (*see* Acidosis and Alkalosis). The carbonates and the alkaline phosphates of the blood and tissues form the alkaline reserve, while the carbonic acid and phosphates the acid reserve. These act as "buffers" and tend to neutralise any attempt to change the actual reaction.

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The importance of the knowledge of *p*H of the different tissues of the body to the pharmacologist is great. Action of drugs which are supposed to have a selective affinity for certain organs or tissues often depends upon their *p*H reaction. Thus Acton has shown that at *p*H of 8, quinine kills paramœcium at a dilution of 1 in 10,000 ; while a concentration of 1 in 100,000 is necessary at *p*H of 7. Dale has shown that emetine in large doses failed to cure dysentery in kittens, produced by strains from man, while these men were cured by a course of emetine. It is possible that the *p*H of the human gut is responsible for the effect of emetine. In fact emetine acts ten times more powerfully, if the acidity of the gut, which has a *p*H of about 6.2 in amœbic dysentery be reduced or rendered alkaline to a *p*H of 8. It is therefore argued that besides the drug and the infective organism (*E. hystolitica*) other factors have to be considered in the cure of amœbic dysentery, and this missing factor is supplied by the host as the result of interaction between emetine and tissues. It has been found that a dilution of emetine hydrochloride 1 in 5,000,000 is lethal to *E. hystolitica* in *vitro* within four days with a *p*H of 6.4, while its potency is considerably reduced with a greater acidity. It is clear, therefore, that the action of drugs in certain instances is modified or intensified by the *p*H reaction of the particular organ over which they produce the main effect.

GROUP I

THE ALKALIES AND METALS OF ALKALINE EARTH

Potassium, Sodium, Ammonium, Lithium, Calcium, Magnesium, Barium

Before discussing the action of the individual drugs of this group we had better consider their therapeutic uses from a broad point of view. Certain salts of the alkalies—potassium, sodium, ammonium and lithium, and some of the salts of the alkaline earths—magnesium and calcium, are employed therapeutically as *antacids*. The salts of the former being rapidly absorbed from the alimentary canal, manifest after a local action in the stomach, certain systemic action, whereas the salts of the latter are absorbed with difficulty and exhibit an active action on the intestinal tract, magnesium being laxative, calcium constipating. Some of the alkaline salts are strong caustics, while others are mild antacids. The former are chiefly the hydroxides of potassium and sodium, and the oxide of calcium. These act by dissolving albumin, extracting water and saponifying fats, while the others, *viz.*, the carbonates and bicarbonates of potassium, sodium, and lithium, and the carbonates and

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oxides of magnesium and carbonate of calcium act merely as antacids. Some are not locally antacids, but break down into carbonates in the blood and tissues and thus increase the alkalinity of the blood, and are therefore systemic alkalisers. They are the acetates, citrates and tartrates of sodium and potassium.

Barium, though it belongs to the group of metals of the alkaline earth, has none of its properties common with calcium and magnesium, except that it is absorbed with difficulty by the epithelial cells.

Antacids are therefore of two types :

1. *Those of alkaline reaction,* viz. (*a*) the caustic alkalies ; and (*b*) the milder alkalies.
2. *Those not of alkaline reaction.*

POTASSIUM

Potassium salts are present in large quantity in both animal and vegetable foods, and although they are absorbed in large amounts very little ill effects are observed. In fact about 2 to 3 ounces are daily ingested with the vegetable food without any specific action of potassium ion being elicited, because the salts diffuse very rapidly through the cells and are excreted very quickly. It is only when the salt is given intravenously, or subcutaneously that the specific effects of potassium ion are observed.

In frogs the muscular movements become first weak and then abolished. In mammals the effects are characterised by muscular weakness and apathy with rapid and laboured respiration from anæmia of the centre.

It is a powerful depressant to the heart, which becomes slow and weak. The systole becomes weaker and the heart of a frog stops in diastole. Injected intravenously it causes a rapid fall of blood pressure and slowing of the heart, accompanied by dilatation and heart block. These effects are due to the direct action of the drug on the heart muscle and not to any effect on the vagus mechanism. When injected into an artery instead of into a vein it causes a sudden rise of blood pressure from peripheral vaso-constriction due to its direct action on the muscles of the vessels.

The same depressant effect is observed when the drug is applied directly on the voluntary muscle. This effect is antagonised by calcium, barium and veratrine. On the plain muscle it diminishes the autonomic movement throughout the body.

POTASSII HYDROXIDUM

Potassium Hydroxide. KOH

Syn.—Caustic Potash ; Potassa Caustica.

Source.—Obtained by the electrolysis of an aqueous solution of potassium chloride. It contains not less than 85 p.c. of pure potassium hydroxide.

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Characters.—Deliquescent, corrosive, alkaline, white sticks, or fused masses. *Solubility.*—In 0·95 part of water, and in 3 parts of alcohol (90 p.c.).

Incompatibles.—Acids, heavy metals, alkaloids.

Official Preparation

1. **Liquor Potassii Hydroxidi.** *Syn.—Liquor Potassæ.*—5 gms. of potassium hydroxide in 100 mils of water. A colourless, odourless, strongly alkaline liquid, with sp. gr. 1.045. *Impurities.*—Carbonates, sulphates, chlorides and other metals.

Non-official Preparation

1. **Pasta Potassæ et Calcis.** *Syn.—Vienna Paste.*—Caustic potash and quicklime in equal weights. Add alcohol or glycerin *q.s.* to form a paste.

SODII HYDROXIDUM

Sodium Hydroxide. KOH

Source.—Obtained by the electrolysis of an aqueous solution of sodium chloride.

Characters.—White sticks, fused masses or scales; dry, hard, brittle, showing crystalline fracture. Deliquescent; strongly alkaline and corrosive. Rapidly absorbs CO_2. *Soluble* in 1 part of water, freely in alcohol (90 p.c.).

POTASSII BICARBONAS

Potassium Bicarbonate. $KHCO_3$

Source.—Obtained by saturating a strong aqueous solution of potassium carbonate with carbon dioxide. Contains not less than 99 p.c. of pure potassium bicarbonate.

Characters.—Colourless, transparent, monoclinic prisms, or white granular powder. Taste, saline, feebly alkaline. *Solubility.*—1 in 4 of water. Almost insoluble in alcohol (90 p.c.).

Incompatibles.—Acid substances, alkaloids and magnesium sulphate.

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

N.B.—20 parts by weight are neutralised by 14 parts of citric and 15 of tartaric acid.

POTASSII CARBONAS

Potassium Carbonate. K_2CO_3

Syn.—Salt of Tartar.

Source.—Obtained by the interaction of potassium sulphate and calcium carbonate. Contains not less than 99 p.c. of pure potassium carbonate.

Characters.—A white crystalline powder. Taste, strongly alkaline. *Solubility.*—1 in 1 of water. Insoluble in alcohol (90 p.c.).

B.P. Dose.—2 to 5 grs. or 0·12 to 0·3 grm.

SODII BICARBONAS

Sodium Bicarbonate. $NaHCO_3$

Source.—May be obtained by the interaction of sodium chloride and ammonium bicarbonate.

Characters.—In white powder, or small, opaque, monoclinic crystals, with saline taste. Slightly alkaline. *Soluble*, 1 in 11 parts of

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water. *Twenty grammes neutralise* 16.7 *grammes of citric acid, or* 17.8 *grammes of tartaric acid.*

Incompatibles.—Acids and acid salts, *e.g.*, bismuth subnitrate heavy metals, alkaloidal salts.

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

SODII CARBONAS

Sodium Carbonate. $Na_2CO_3,10H_2O$

Syn.—Soda or Washing Soda.

Source.—Obtained by action of heat on sodium bicarbonate, and subsequent crystallisation from water. Contains not less than 99 p.c. of pure sodium carbonate.

Characters.—Transparent, colourless, rhombic crystals. Efflorescent. Taste, strongly alkaline; odourless. *Soluble* in 2 parts of cold water. *Twenty grammes neutralise* 9.8 *grms. of citric acid, or* 10.5 *grms. of tartaric acid.*

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

SODII CARBONAS EXSICCATUS

Exsiccated Sodium Carbonate

Syn.—Sodii Carbonas Monohydratus, U.S.P.

Source.—Obtained by action of heat on sodium bicarbonate. Contains not less than 99.5 p.c. of pure anhydrous sodium carbonate.

Characters.—A dry, white powder; odourless. Taste, strongly alkaline. Readily *soluble* in water.

B.P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

Pharmacology of Caustic Potash, Caustic Soda, Carbonates and Bicarbonates of Potassium and Sodium

Externally.—Applied to the skin a concentrated solution of caustic potash or caustic soda acts as a powerful **irritant** and **caustic.** It has a strong affinity for water and dissolves albumin. The solutions of carbonates are less caustic than the hydroxides. A weak solution of caustic potash or a solution of carbonate will soften the skin, dissolve the oily secretions of the glands and cleanse the surface more thoroughly than plain water. Applied for some time they penetrate more deeply and cause irritation and redness. Caustic potash and caustic soda are therefore **rubefacient, antacid** and **detergent.**

Internally. **Gastro-intestinal tract.**—The hydroxides and the carbonates have an alkaline taste and dissolve the superficial layers of the lining membrane and the mucous secretions in the mouth. Concentrated solutions may cause deep erosions as on the skin, while very dilute solutions only excite a **reflex flow of saliva.** In the stomach the hydroxides and the carbonates exert the same corroding effect when given in concentrated solutions; in dilute solutions they are **mild irritants** and may cause **gastritis.** The bicarbonates produce no such effect on the stomach. They

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dissolve mucus and neutralise acid, but their effect like all alkalies will vary greatly according to the nature of the stomach contents at the time of administration. Given during the digestive period they have the following definite effects, *viz.*—

(*a*) reduce the gastric secretion,

(*b*) neutralise some of the hydrochloric acid,

(*c*) liberate CO_2 gas, which acts as a carminative; and

(*d*) inhibit gastric movement and delay the opening of the pyloric sphincter.

The effect on gastric secretion is not quite clear. It is claimed that given during digestion they only diminish acidity temporarily, followed by a rise above normal. Indeed some hold that while alkalies inhibit gastric secretion when given before meals they increase the secretion when administered during the meals. This is possibly due to the liberation of CO_2, for Pawlow observed that gastric secretion was increased by the presence of CO_2. Dilute solutions act as mild irritants to the stomach walls and thus improve the circulation, help expulsion of gas, and reduce pain and distension much in the same way as any other mild irritants like volatile oils.

In cases of fermentation, by neutralising the organic acids which tend to cause pyloric spasm, they relieve that condition.

In the intestine the alkalies by neutralising or diminishing the acidity of the gastric contents has a retarding influence on the pancreatic secretion, which is normally stimulated by the passage of a highly acid fluid from the stomach, although the greater alkalinity of the intestinal contents tends to increase the efficiency of the pancreatic juice already secreted. In hyperacidity, however, the alkalies render the contents of the intestine less irritating and thus have a tendency to allay catarrh. Stadelmann has shown that alkalies have no effect on the secretion of bile, and are not excreted in it, and do not cause any change in its reaction. Very large single doses cause vomiting. Repeated large doses open the bowels; the bicarbonate of soda sometimes acting as a purgative.

Blood.—All these salts are freely absorbed and rapidly excreted. They are neutralised by the CO_2 in the tissues and circulate as neutral bicarbonate. The reaction of the blood remains unchanged, but the alkali available for the neutralisation of acid is augmented. If given for any length of time, they cause the quality of the blood to deteriorate and reduce the body weight.

Alkalies increase oxidation *in vitro*, and for this reason they have been credited with an action on metabolism. But they do not increase the alkalinity of the tissues to any large extent and are very soon excreted by the urine. The

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estimation of nitrogen metabolism has yielded different results. Similarly they are supposed to favour oxidation of fats and proteins causing an increased consumption of oxygen and excretion of carbonic acid. The question of oxidation of tissues has also recieved much attention by different investigators, but the results were contradictory. In fact tissue waste is not increased by alkalies.

Heart and circulation.—It has been thought that potassium salts are muscular depressants and therefore tend to slow and weaken the heart. But in therapeutic doses given by the mouth these salts are non-depressant and inert. In this country (India), where a vegetable diet is widely used, very large quantity (1½ to 3 oz.) of potassium salts are ingested daily without any such effect, and, as pointed out by Dixon, they are excreted so rapidly that we get no specific action. In practical therapeutics potassium salts may be regarded as equivalent to the corresponding sodium ones, except when they are injected intravenously.

Respiratory tract.—These salts stimulate the bronchial secretion, and make the mucus less viscid. They are therefore **expectorants**. Potassium iodide possesses this property in a very marked degree.

Kidneys, etc.—Both the bicarbonates and the carbonates as well as the vegetable potash salts, are eliminated as carbonates, and in this way they stimulate the secretion of urine, and are therefore **diuretics**. They also **alkalise** the urine and thereby increase its capacity of holding more **uric acid in solution**. Passing over the mucous membrane of the genito-urinary tract, they either exercise a direct sedative action on it, or by rendering the urine alkaline soothe any irritation that may be present.

Toxic doses of alkalies, or when continued in large doses, cause alkalosis giving rise to headache, vomiting, general prostration and possibly tetany due to diminished calcium in the plasma.

Toxicology of the Caustic Alkalies

Persons are not often poisoned by the caustic alkalies, but accidents occasionally happen through their swallowing by mistake either *pearlash*, which is a mixture of potassium carbonate and potash, or *soap-lees*, which contains the corresponding sodium salts.

The symptoms are a caustic taste in the mouth and burning heat in the throat, the mucous membrane of which becomes swollen, soft, and red. This is followed by pain in the stomach, vomiting, sometimes of blood, diarrhœa, feeble pulse, general collapse from shock. On post-mortem examination, the whole mucous membrane from the mouth to the stomach is found red, swollen and excoriated.

Recently several cases of poisoning by caustic soda were recorded by Willimott and Gosden (*British Medical Journal*, June 9, 1934) from Cyprus, most of which were suicidal. The symptoms were burning pain in the mouth, throat and stomach with exhaustion and shock. Some had vomiting of blood, perforation of the œsophagus and stomach.

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If recovery occurred there was stricture of the œsophagus and pylorus. Post mortem showed necrosis of the liver and kidneys.

Treatment.—Any rapidly acting emetic, or a hypodermic injection of apomorphine. If no emetics are available, give copious draughts of warm water and tickle back of throat with a feather. After vomiting has occurred give (1) **feeble acids** (*e.g.*, vinegar, lime-juice dilute acetic acid or citric acid); (2) **demulcents** (oil, linseed tea, white of egg).

N.B.—Do not wash out the stomach with the stomach-pump as there is danger of damaging the softened mucous membrane.

Therapeutics of Caustic Potash, Caustic Soda, Carbonates and Bicarbonates of Sodium and Potassium

Externally.—Caustic potash in the form of the solid stick is occasionally applied to remove growths such as **warts**, or to destroy **lupus**. Being very deliquescent its action spreads to the surrounding and deeper tissues and it is necessary to protect the tissues by applying blotting paper to absorb moisture. Acetic acid or vinegar diluted should be applied to neutralise the caustic when further action is not required. As it has been found that it often caused severe caustic action, the application of **Vienna Paste** has been recommended as its action is milder and is more manageable. Cotton wool soaked in liquor potassæ and applied over an ingrowing toe-nail makes it soft enough to be peeled off easily. A solution of the bicarbonate (1 dr. to 1 pt.) allays itching of many skin diseases, such as **urticaria**, etc., and as an injection arrests the discharge of **leucorrhœa**. A weaker lotion checks the weeping of raw, red **eczema**. For this purpose a piece of lint soaked in the lotion is applied to the raw surface and then covered with oil silk to check evaporation. Alkalies are useful in **insect bites.**

Internally.—While alkalies are either indifferent or disturbing to normal digestion, they are of great value in digestive troubles. In **dyspepsia**, where the gastric secretion has become thin and watery, the bicarbonates are given a few minutes before food; and when there is epigastric pain, heartburn or acid eructations, they are best administered after food. In **gastric irritability**, or to render the **blood and urine alkaline**, they are given in effervescing form. In cases of **chronic gastritis**, such as the alcoholic form, lavage of the stomach with alkalies is of value to clear the stomach of its mucus and prepare it to receive food. For this purpose the bicarbonate of soda is commonly used (1 dr. to 1 pint of hot water). Given about twenty minutes before food it tends to call forth the "appetite juice" and is often combined with aromatics and bitters. In cases of **hyperchlorhydria** and **duodenal ulcer** it will relieve the pain if given two hours or more after the meals, and when there is much fermentation

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and formation of organic acids it is often useful when given shortly after eating. As the gastric juice is subsequently increased it is combined with carbonate or oxide of magnesium and carbonate of calcium.

Although alkalies have no direct effect in increasing the secretion of bile they are used in jaundice often with benefit. This it does by relieving the catarrh of the intestine which causes obstruction of the bile duct.

When a systemic action is required alkalies are best given on an empty stomach. In severe acidosis, such as may be in **delayed chloroform poisoning, cyclical vomiting of pregnancy,** very large doses are given by the mouth, by the continuous rectal drop method, or intravenously, of course remembering that sodium salts are preferable to the corresponding potassium salts. It is valuable in **diabetic coma.** The daily dose should be 1 to $1\frac{1}{2}$ oz. freely diluted, and should be continued until the *p*H of the plasma is normal, and if possible until the reserve alkalinity of the plasma has been restored. Large doses have the disadvantage of producing looseness of the bowels. The use of bicarbonate should not be delayed till coma has actually set in, but should be given as soon as acidosis is recognised. It should be given freely diluted, preferably between meals. When given subcutaneously, the solution containing bicarbonate should not be boiled, as this drives off CO_2 and converts part of the bicarbonate into carbonate which is highly corrosive to the tissues and may produce sloughing. Recently it has been shown that bicarbonate of soda prolongs starvation acidosis even when a large amount of sugar is available in the body, and since the acidosis of diabetes is of the same nature as that induced by starvation, some hold that the use of bicarbonate of soda will be detrimental in this condition. Bicarbonate of soda is added to saline solution for injection in cases of **cholera** (*see* sodium chloride). Alkalies have also been used in diabetes on the idea that they help oxidation of tissues, and by promoting combustion of sugar reduce the glycosuria. There is no reason to believe that they increase oxidation of tissues at all, and diabetes is not due to deficiency on the part of the tissues to oxidise sugar.

Formerly the alkalies were largely used in rheumatism on the idea that they help excretion of uric acid. Similarly patients suffering from **gout** are treated with alkaline mineral waters. In both these conditions improvement follows but the precise nature of their action is not known and the explanation so far given is not conclusive. According to Von Noorden alkalies are not only useless in this disease but positively harmful.

As an antidote to poisoning by caustic acids, the carbonates and the bicarbonates are to be avoided as they create

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carbonic acid gas and so cause risk of rupture of the stomach. Caustic potash and other alkaline salts may be used in these cases.

Alkalies, especially the bicarbonates, are largely used either alone or with other **expectorants** to lessen the viscidity of the secretion in **bronchitis** and **bronchial catarrh.** Indeed potassium bicarbonate is a common ingredient in most cough mixtures.

They render the urine alkaline in cases of excessive acidity of the urine. But as the urine tends to become acid, it is necessary to give alkalies in large doses (2 to 4 drs. of the bicarbonate) daily. Since the *coli* organisms do not grow freely in an alkaline medium, alkalies are lagely used in **B. coli infection** of the urinary tract, but to be of any use large doses have to be given. These large doses of bicarbonates however often cause diarrhœa or irritation of the stomach, therefore citrates and acetates are preferred. As they hold more uric acid in solution they are used in uric acid diathesis and uric acid calculi often with good results. It should be kept in mind that excessive alkaline urine will cause deposit of phosphates in the bladder and thus may tend to increase the formation of calculus, though not of the same variety.

Large doses of bicarbonate may cause retention of water and produce œdema. This may occur even in healthy persons and is probably analogous to salt œdema. They may also cause *alkalosis* with injury to the kidneys and retention of nitrogenous elements in the blood.

Prescribing hints.—Always prescribe the carbonate of bismuth with bicarbonate of soda and not the subnitrate, which will liberate carbonic acid gas in a mixture. The bicarbonate should be used in preference to the carbonate, and the salts of sodium in preference to potassium. Bicarbonate of soda administered with sodium salicylate tends to prevent precipitation of the irritating acid and prevents acidosis.

POTASSII ACETAS

Potassium Acetate $CH_3.COOK$

Source.—Prepared by fusing the product of the interaction of acetic acid and potassium carbonate. Contains not less than 99 p.c. of pure potassium acetate.

Characters.—White foliaceous, satiny masses, or granular particles; deliquescent. Taste, sharp, saline; odourless, or with a faint acetous odour. *Solubility.*—2 in 1 of water, 1 in 2 of alcohol (90 p.c.).

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

Non-official Preparation

1. **Mistura Potassii Acetatis Composita, B.P.C.** *Syn.—Mistura Diuretica.*—Each fluid ounce contains potassium acetate, 20 grs.; spirit of nitrous ether, 30 ms.; tincture of hyoscyamus 20 ms.; succus

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scoparium 1 dr.; with infusion of buchu. *Dose.*—½ to 1 oz. or 15 to 30 mils.

POTASSII CITRAS

Potassium Citrate. $K_3C_6H_5O_7,H_2O$

Source.—Prepared by the interaction of citric acid and potassium carbonate. Contains not less than 99 p.c. of pure potassium citrate.

Characters.—White, granular crystals, or a crystalline powder. Odourless; taste, saline. *Solubility.*—Freely in water.

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

SODII CITRAS

Sodium Citrate. $C_6H_5O_7Na_3, 2H_2O$

Source.—Obtained by the interaction of citric acid and sodium carbonate.

Characters.—White granular crystals, or crystalline powder with a saline taste. No odour. Slightly deliquescent in moist air, efflorescent in dry air. *Soluble* in less than 1 part of water, insoluble in alcohol (90 p.c.).

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

Pharmacology of Acetates and Citrates of Potassium and Sodium

Externally.—All these salts are neutral and have none of the antacid or caustic properties of liquor potassæ or alkaline salts.

Internally. **Gastro-intestinal tract.**—Acetates and citrates do not irritate the stomach and are easily borne. Being neutral they are not direct antacids like the carbonates and bicarbonates, but act as *remote antacids.* The citrates are absorbed less readily than the acetates.

Blood.—These salts are converted into bicarbonates, in the body, $KC_2H_3O_2+4O=KHCO_3+CO_2+H_2O$; and thus exert an alkaline action after absorption. They have therefore the same action after absorption as alkalies, except that they do not act as direct antacids. When introduced directly into the blood the citrate inactivates calcium by forming double salts which do not liberate calcium ion, and produce typical effects of calcium deprivation. In moderate doses (10 to 50 c.c. of 10 p.c. solution in man), given intravenously, sodium citrate shortens the coagulating time of the circulating blood. The mechanism of this action is not clear and has been attributed to injury of the blood platelets leading to liberation of thromboplastin, or to peripheral vaso-constriction, accumulation of thrombocytes and leucocytes in the splanchnic area which accelerate hæmostasis.

Kidneys.—They are all **diuretics** and render the urine alkaline. Although the urine becomes alkaline yet the total amount of acids eliminated is increased. They have very slight effect on the flow in health.

Skin.—They are all **diaphoretics,** but the method of this action is obscure.

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THERAPEUTICS OF ACETATES AND CITRATES OF POTASSIUM AND SODIUM

Internally. **Gastro-intestinal tract.**—The nascent citrate is a powerful gastric sedative and is prescribed in cases of gastric irritability. The carbonate or bicarbonate is generally used with citric acid in an effervescing form. Sodium citrate is largely used as an addition to milk (2 to 5 grs. to the ounce) to render the clots more flocculent and therefore more easy of digestion. The citric acid prevents the ionic action of calcium and the curd consisting of sodium caseinate is much softer than calcium caseinate. Hence it is largely used in the curd **indigestion of children** and **diarrhœa** of infants. Given in large doses it causes œdema which disappears on witholding of the drug.

Blood.—These salts were formerly used in the treatment of **gout** and **rheumatism.** They act like the alkaline carbonates or bicarbonates but do not irritate the stomach or neutralise the gastric secretion. Sodium citrate is used in large doses to raise the alkalinity of the blood in conditions of **acidosis,** *e.g.* in **diabetic coma,** without upsetting the stomach or causing diarrhœa which very often happens when bicarbonate of soda is used in large doses. Because it shortens the coagulating time, sodium citrate (9 grm. in 30 p.c. solution intramuscularly, or 6 grm. in 10 p.c. solution intravenously), has been recommended for the control of **bleeding during operation** or to stop bleeding in **gastric** or **duodenal ulcer.**

Kidneys.—All these salts are used to make the urine alkaline. Thus they are used to prevent precipitation of uric acid in cases of **uric acid diathesis** and also to dissolve small uric acid calculi in the kidneys or bladder. Sir William Robert warns us against using more than 40 to 60 grs. of acetate or citrate in 4 oz. of water, every 4 hours. for he says that in larger doses they may cause formation of insoluble biurates on the surface of the stones. They are largely used in febrile conditions for their diaphoretic and diuretic properties, and also in general anasarca. By reducing the acidity of the urine they relieve irritability of the bladder, and are used in **cystitis,** and **gonorrhœa** in the early stage, and to prevent frequent micturition. For the same reason they are used in *B. coli* infection of the urinary tract, but large doses are required to maintain the alkalinity of the urine.

Lungs.—Because they are converted into carbonates in the blood they are used as expectorants in bronchial troubles to make the secretion less viscid.

POTASSII CHLORAS

Potassium Chlorate. $KClO_3$

Source.—Obtained by the electrolysis of a hot solution of potassium chloride. Contains not less than 99 p. c. of potassium chlorate.

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Characters.—A white powder, or colourless crystals; taste, cool and saline. With organic or oxidisable substances liable to explode if heated. *Solubility.*—1 in 16 of cold, 1 in 3 of boiling water.

Incompatibles.—Explodes when rubbed with sulphur, sulphides, charcoal, sugar, tannic acid, ammonium chloride, or glycerin. Mineral acids, ferrous salts.

B. P. Dose.—5 to 10 grs. or 0·3 to 0·6 grm.

Non-official Preparation

1. **Gargarisma Chlori, B.P.C.** *Syn.—Chlorine Gargle.*—Pot. Chloras 22·9 grm., Acid Hydrochlor. 4·2 mils, Distilled Water to 1000 mils. Generate chlorine gas by mixing chlorate and acid, and dissolve gradually in water.

Pharmacology

Externally.—Coming in contact with a septic surface or discharge, the chlorate is decomposed, and oxygen is liberated. This nascent oxygen then acts as a **stimulant** and **antiseptic to septic tissues**, but it is not an antiseptic in the ordinary sense of the term, as outside the body it has very little effect even upon the most sensitive bacteria.

Internally. **Gastro-intestinal tract.**—In small doses, potassium chlorate has no action, but in concentrated solution it may through its local salt action cause severe nausea and vomiting, and after absorption considerable diuresis may arise from a similar action on the kidney.

Heart and circulation.—It has a specific action on the blood, and after a moderately large dose it disintegrates the red blood-corpuscles and converts hæmoglobin into methæmoglobin, which is set free in the serum. This effect is also observed when chlorate is added to a little drawn blood and shaken up, the mixture soon becoming reddish brown (chocolate colour) and shows the spectrum of methæmoglobin and later of hæmatin. Since other oxidising agents produce the same effect, this action has been attributed to the oxidising property of the chlorate, but the salt is very stable and hardly possesses any oxidising power at body temperature. When this change takes place in the vessels the oxygenating power of the blood is reduced and asphyxia threatens. When however sufficient hæmoglobin remains to continue the respiration of the tissues the subacute form of poisoning results from hæmolysis. As a result of which the renal tubules become blocked with masses of hæmoglobin and fragments of the corpuscles, causing either casts to appear in the urine, or total suppression.

Kidneys.—In moderate doses (15 to 20 grs.) it acts as a diuretic, and more powerfully during pregnancy. In toxic doses, the kidneys become congested, the urine becomes bloody or dark-coloured, and at last there is complete suppression due to blockage of the tubules with degenerated corpuscles. Death occurs usually from uræmia.

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Elimination.—Very little is utilised in the blood and tissues, so that about 90 p.c. of the amount given is recovered from the urine. It is also excreted from the saliva, sweat, milk, tears, and nasal mucus.

Toxic action.—It may give rise to dangerous symptoms in individuals after a single large dose, or from repeated small doses. 15 grs. caused death in a child, while an ounce has been taken without any bad effect. The toxic symptoms are nausea, vomiting, diarrhœa, scanty urine or complete anuria, urine becoming a deep reddish-brown colour due to the presence of hæmoglobin, methæmoglobin and hæmatin in solution. Icterus may appear, and the patient may die from uræmic symptoms even as late as a week after the first symptoms. All these symptoms are dependent on the action of the chlorate on the hæmoglobin of the red blood-cells. Death may result from two causes:

1. From respiratory failure and *asphyxia*, by a rapid breaking down of the red blood-cells and resulting inability of the blood to carry a sufficiency of oxygen.
2. From *urœmia*, owing to complete or partial suppression of urine following on obstruction of the renal tubules, by hæmoglobin and fragments of corpuscles.

THERAPEUTICS

Locally.—The chief local use of potassium chlorate is in the treatment of different mouth and throat troubles, such as **aphthous stomatitis, follicular tonsillitis,** and in the tenderness and inflammation of the gums which follows the prolonged use of mercury. How it acts is not clearly understood, and the theory of its acting as an oxidising agent can hardly be explained on any rational ground. It is possible that its effects are due to salt action. A lotion (10-15 grs. to 1 oz. of water or any astringent infusion) is used as a gargle for such cases. Tablets or lozenges, of which many kinds combined with borax and cocaine are on the market, may be slowly sucked in hoarseness of the throat.

These catarrhal conditions of the mucous membrane of the mouth and fauces are greatly benefited if the local treatment is accompanied by internal administration, for the salt is excreted with the saliva after absorption, and thus locally influences the disease. Sometimes it is useful in cases of **habitual abortion**. The late author considered this drug to be a valuable diuretic in the **suppression of urine in cholera.**

Prescribing hints.—Potassium chlorate, being a strong oxidising agent, when prescribed with syrup of ferrous iodide, liberates iodine and forms a preciptate of hydroxide of iron. With iodide of potassium it forms a poisonous compound in the body probably iodate of potassium.

POTASSII NITRAS

Potassium Nitrate. KNO_3

Syn.—Purified Nitre; Saltpetre. **Syn. I.V.**—*Sora*, Beng. *Shora*, Hind

Source.—May be obtained by the interaction of sodium nitrate and potassium chloride.

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Characters.—White, crystalline powder, or colourless crystals. Taste, cool, saline. *Solubility.*—1 in 4 of water. *Impurities.*—Chlorides sulphates, lime.

B.P. Dose.—5 to 15 grs. or 0·3 to 1 grm.

Non-official Preparations

1. **Charta Nitrata, B. P. C.** *Syn.—Saltpetre Paper.*—Made by saturating white blotting paper in a 20 p.c. solution of nitre. The fumes are inhaled in *asthma*. **Ozone Papers** are similar in composition.

2. **Pulvis Lobeliæ Comp., B.P.C.** *Syn.—Asthma Powder.*—Potassium Nitrate 25, Boiling Distilled Water 25, dissolve and soak a mixture of Lobelia and Stramonium leaves in coarse powder each 25, Tea leaves in coarse powders 25. Mix well, dry, and add oil of anise 0.1. One teaspoonful may be burnt to fumigate a bedroom, or the fumes inhaled in *asthma*. This is a supposed imitation of **Himrod's, Bliss's, and the Green Mountain Cure.**

Pharmacology

Internally. **Gastro-intestinal tract.**—It has a cool saline taste, and in ordinary doses taken in concentrated solution may give rise to **gastro-enteritis**, with the presence of blood in the vomit and stool, muscular weakness, collapse, even coma and death. The same large doses if taken freely diluted cause none of these symptoms. The nitrates differ from other salts by possessing some further irritant action, and this irritant effect has been thought to be due to the reduction of the nitrate in the intestine and tissues into the poisonous nitrite. This explanation is however open to doubt. In large doses most of it is excreted as nitrate in the urine and some passes out with the saliva and sweat.

Heart and blood.—Contrary to other potash salts, it is a **powerful depressant** to the heart, rendering its action slower and weaker. It destroys the normal oxygenating powers of the red blood-corpuscles, and outside the body prevents the **coagulability** of the blood.

Skin and kidneys.—It is slightly **diaphoretic**, but has a powerful **diuretic** action. Diuresis is due partly to **salt action** which increases the exchange of fluids between the blood and lymph, thus promoting the filtration in the kidney. Practically the entire quantity is excreted unchanged, a small portion may be reduced to nitrites.

Therapeutics

Internally.—Now-a-days its use is almost discrarded. Formerly it was employed in almost every **febrile and inflammatory** disease, but now only on rare occasions. It is no longer used in **rheumatism**, but it is a useful remedy for arresting the onset of a **gouty attack**, or for removing the headache due to a debauch. 20 grs. of nitrate with 30 grs. of potassium bicarbonate in a tumbler of soda water is the best method of administration in

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such cases. As a diuretic it is chiefly used in conjunction with other diuretics, but the acetates and citrates are always preferred. As an inhalation it cuts short an **asthmatic fit**, and hence it is the basis of many nostrums, such as Himrod's Cure, Green Mountain, etc. Charta nitrata or charta nitrata et chlorata can be burnt, and the fumes inhaled.

Caution.—Its use is to be avoided in inflammation of the stomach, intestines, bladder and kidneys, and cardiac weakness.

SODII CHLORIDUM

Sodium Chloride. NaCl

Syn.—Common Salt.

Source.—May be obtained by purifying common salt.

Characters.—Small white, crystalline powder, or transparent, cubical crystals, free from moisture. Taste, saline. Odourless. *Solubility.*—1 in 3 of cold water.

Official Preparations

1. **Injectio Sodii Chloridi et Acaciæ.**—Sodium chloride 0.9 p.c. and acacia 6 p. c.
2. **Liquor Sodii Chloridi Physiologicus.** *Syn.—Normal Saline Solution*; *Physiological Saline Solution.*—Sodium chloride 0.9 p.c. Should be prepared with sterilised water for intravenous injection, and should be used within twenty-four hours of its preparation.

Non-official Preparations

1. **Liquor Dextrosi et Sodii Chloridi, B.P.C.** *Syn.—Glucose-saline Solution.*—Dextrose, 50; sodium chloride, 9; sterile water to 1000.
2. **Liquor Ringer, B.P.C.** *Syn.—Ringer's Solution.*—Sodium Chloride 7.0; potassium chloride, 0.14; calcium chloride, 0.12; sodium bicarbonate, 0.2; distilled water to 1000.
3. **Liquor Ringer-Locke, B.P.C.** *Syn.—Ringer-Locke Solution.*—Sodium chloride, 9.0; potassium chloride, 0.42; calcium chloride, 0.24; Dextrose, 1.0; sodium bicarbonate, 0.5; distilled water to 1000.

Pharmacology

Sodium chloride is an essential constituent of the body and perhaps the chief mineral constituent of the blood serum. It is therefore essential that the necessary supply of this substance should be introduced either with the food itself, or as an addition to the food. As it is always present in the body in large quantities and exerts no specific action, it presents a perfect example of **salt action** which action varies in proportion to the concentration of salt in solution.

This salt action only affects living tissues by changing the physical properties of the fluids contained in them or surrounding them. In the body the epithelial cells of mucous membranes, the endothelial cells of vessels, and the cells

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of the renal glomeruli act as semipermeable membrane, *i.e.*, a membrane through which the solvent can pass, but none or very little of the dissolved substance. If two equimolecular solutions are separated by such a semipermeable membrane, the osmotic pressure is equal on the two sides, and the solutions are then said to be isotonic, and no exchange of constituents occur between the two fluids. Pharmacologically the term *isotonic* means a solution having the same osmotic tension as that of the blood. If however a given volume of one of these fluids has a higher molecular concentration than the other, it is said to be *hypertonic* (or hyper-isotonic), and an interchange between the two fluids takes place, water being attracted from the hypotonic to the hypertonic solution, and to a smaller extent the substances held in solution pass from the hyper to the hypotonic solution, thus shortly rendering the two fluids once more isotonic.

In the human body with its already noted semipermeable membrane the process of osmosis is continually going on whenever fluids of varying tonicity meet. As an example, red blood cells shrink in size when they are placed in a solution of salt stronger than blood plasma (hypertonic), because the water is withdrawn from them. In hypotonic solution they swell up as they absorb water and eventually burst liberating hæmoglobin to the surrounding tissues; while in isotonic solution they remain unaltered in size.

The muscles are similarly affected, hypertonic solutions withdraw fluid, while weaker ones are absorbed into the muscle. As the muscles are rendered dry and hard, and thus unsuitable for microbic growth, salting is used in the preservation of meat and fish. Strong salt solutions by withdrawing their fluid contents irritate the exposed nerves.

As these osmotic exchanges are continually going on in the human body, its importance in the preservation of the balance of the constitution of the body fluids can hardly be exaggerated, and as has been pointed out it is purely a physical process which goes on passively without the expenditure of vital activity which entails a drain of energy of the organism. Thus the process of osmosis may be regarded as a great conservator of energy, of respiratory interchange, and metabolism.

Salt has a characteristic taste and strong solutions are astringents. It has very little effect on digestion, and the absorption of food is very little altered when salt is added to food It is possible, however, that a small quantity of salt in the food may render it more palatable and thus induce a reflex flow of gastric juice. Large concentrated solutions irritate the stomach and act as **emetics**. Very little is absorbed from the stomach. Being of lower osmotic pressure than the blood serum hypotonic solution is absorbed from the bowel readily. Isotonic solution is more slowly absorbed;

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while hypertonic solution is absorbed with difficulty, not till it has withdrawn fluid and increased in volume to make it isotonic.

Blood.—The changes on the blood after an intravenous injection depends upon the nature of the solution used, whether *isotonic*, *hypertonic*, or *hypotonic*. When a hypertonic solution is used, by osmotic attraction it draws more lymph into the blood to regain its normal composition, this increased volume of the blood in its turn tends to augment the flow of lymph, urine and sweat; and since the normal balance of plasma and corpuscles must be restored, it sets up currents between the blood and the fluid of the surrounding lymph. All these changes are accompanied by a large rise of capillary pressure in the abdominal viscera, and it is possible that the inward flow of lymph is the outcome of this pressure.

As a result of these changes in the blood and lymph there is an increased activity of the excretory organs. Thus there is a copious **diuresis** following an injection of salt solution. It has been suggested that diuresis is the result of increased volume of blood and lymph causing an inward capillary pressure in the glomerulus which promotes the escape of fluid into the capsule. But the more plausible explanation is that the presence of salt and water in excess in blood, following an injection, leads to an increased interchange of water between the tissues and blood making the latter diluted, thus increasing the non-colloidal constituents of the blood and allowing better filtration and more fluid to pass through the glomeruli into the tubules.

Elimination.—Salt is excreted chiefly by the urine as potassium chloride, a small portion being lost by the fæces and sweat. Its excretion is diminished in some cases of nephritis, in pneumonia and during growth of new tissues (cancer). Its excretion is hastened by the administration of bromides, iodides, nitrates and thiocyanates, while its use hastens the excretion of these salts, and may be useful in bromism and iodism.

Therapeutics

Cold douching with salt and water is a very valuable remedy in all forms of muscular weakness, specially in the weak back of growing girls.

Salt being mild irritant, sea bathing acts as a general stimulant to the skin by improving the circulation and nutrition and produces a reflex tonic effect. This is the common experience after sea bath. If the patient is unable to proceed to the sea side, Tidman's sea salt, or ordinary rock salt (one pound to three gallons of water), is an efficient substitute. It is doubtful if salt baths exert any influence

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on metabolism although it is often recommended in diverse conditions. At Droitwich and Nantwich concentrated hot salt baths (20 p.c.) are used for **chronic rheumatism, sciatica,** and **joint diseases,** where the patients not only have daily baths but drink sufficient water on the idea that the tissues will be more thoroughly washed out and waste products will be removed from the system. It is doubtful if this helps more excretion of uric acid from the system, but the fact remains that patients do show improvement under such treatment. The reasons for improvement are perhaps change of climate, a well regulated life and the faith in the healing power of salt water. Recently French physicians have been treating dyspepsia, wasting, and chronic skin affections of adults, and gastritis and entero-colitis in infants with injections of sea water.

Wright's solution (sodium chloride 4, sodium citrate 1, water 120), or hypertonic saline are used in the physiological treatment of septic wounds, and as lotions for washing ulcers and sinuses, specially in diabetics where strong antiseptics damage the tissue. The usual practice is to pack the wound with gauze soaked in the solution, or to irrigate the wound with the lotion. Efficiency of this treatment is due to the hypertonic saline acting as a lymphagogue, which liberating a tryptic ferment from the leucocytes cleanse the wound and check microbal growth.

Eighty grains (0.9 p.c.) of common salt in one pint of water constitutes normal saline solution, and is isotonic with the blood, which may be injected either into the veins, the rectum, or the loose connective tissue under the axilla or breast, in (1) **shock** or **collapse** from any cause, such as severe hæmorrhage or dehydration, to restore the fluid needed for the heart to work efficiently; (2) certain **toxæmic conditions,** *e.g.*, uræmia or eclampsia; (3) **carbon monoxide poisoning**; (4) **cerebral œdema** and **intracranial pressure**; and (5) profound **malnutrition** and **prostration.** In the treatment of shock its value is not very favourable and the blood pressure is not maintained for long, moreover large injections may cause fatal dilatation of the heart. In temporary collapse its value is better. For the relief of urgent symptoms in cerebral tumour, uræmia, and meningitis, it has been given intravenously (20 c.c. of 20 to 30 p.c. solution). It has been used with less justification in cases of head injury, post-concussional syndromes, and in severe headaches of various types. Improvement resulted when there was definite rise of intracranial pressure. It has however been shown that the fall of pressure is followed by a rise with secondary œdema of the brain due to the fixing of the salt by the brain cells (H. Hoff, *Medical Annual*, 1934). In other conditions of toxæmia it does not help elimination of poison by itself, though it may cause considerable dilution of the poison. It

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is commonly given intravenously, the usual quantity introduced being 500 to 1500 c.c. (1 to 3 pts.). The most commonly employed solution is normal saline containing a full teaspoonful of salt to 1 pint of *ordinary water*, as this usually contains some calcium. If made up with distilled water and given intravenously, pure sodium chloride may have a poisonous effect. The addition of 0·5 p.c. of sodium bicarbonate to the physiological saline solution approaches more closely the normal reaction of the blood, counteracts acidosis and ensures more lasting restoration of the blood-pressure.

The effects of these saline infusions vary according to whether the volume of the blood has been previously decreased or not. If there has been no previous diminution in the volume of the blood, a saline infusion has no effect in raising arterial pressure and may lead to anasarca. On the other hand if the volume of blood has been diminished by hæmorrhage, a saline infusion will not only increase the volume of the blood and so maintain arterial pressure, but by shortening the coagulation time will favour cessation of hæmorrhage.

Since colloids leave the vessels slowly and help to retain the transfused fluid, they diminish diuresis, lymph filtration and œdemas. Acacia and gelatin therefore were added to saline solution to maintain the blood pressure for a longer time in cases of **shock** and **hæmorrhage** than when treated with plain non-colloidal saline infusion. But the results have not been very encouraging, although they appeared to be of some value at first. Severe and even fatal reactions after the use of acacia, some from faulty technique and others from special susceptibility to the drug, have been recorded. It alters the colloidal equilibrium of the blood which tends to agglutination of the corpuscles and to other anaphylactoid phenomena (Hanzlik).

It is very largely used, and with very good results, in the treatment of **cholera**, in which as much as three pints of hypertonic solutions are used. The usual formula for hypertonic solution consists of sodium chloride 120 grs., pot. chloride 6 grs., calcium chloride 4 grs. to 1 pt. of water. To this is added sod. bicarb. 40 grs. and glucose 14 grs. The bicarbonate of soda maintains the alkaline buffer value of the blood and counteracts tendency to acidosis. In cases of severe shock or collapse a small infusion containing adrenaline helps to promote the maintenance of blood pressure. It is also used intravenously, subcutaneously, or per rectum in other forms of dehydration, as for instance in acute bacillary dysentery. Besides overcoming collapse, the chloride combines with the toxins and helps them to be excreted *via* the kidneys. Salines should not be given in any form of œdema, especially that of the lungs.

Internally.—Cold salt and water is an excellent **gargle**

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for **chronic relaxed throat**, and also a very effective nasal douche. It is a prompt and efficient **emetic**, and it may be injected into the rectum for the cure of **thread-worms**. It is an antidote in **poisoning by silver nitrate**, which it converts into the insoluble chloride. It is also useful in cases where a **leech has been swallowed or has got up the nose.**

Note.—Since retention of salt in the tissues may lead to œdema, a salt free diet has been recommended to reduce œdema with salt retention. Salt free diet sometimes lowers blood pressure and has been advised in primary hypertension.

LIQUOR SODII ETHYLATIS

Solution of Sodium Ethylate. (*Not official*)

Source.—By dissolving 1 of sodium in absolute alcohol 20.

Characters.—A syrupy liquid, colourless when fresh, turning brown on keeping.

Uses.—It is used as a **depilatory**, and to **destroy warts, moles, and nævi.** Apply lightly with a pointed glass rod for 2 or 3 successive days till a scab forms. When this falls off, repeat the treatment if necessary. If pain results, allow a drop of chloroform to fall upon the spot.

SODII SULPHOCYANAS

Sodium Sulphocyanate. (*Not official*)

Syn.—Sodium Thiocyanate. Sodium Rhodanate.

Dose.—1 to 5 grs. or 0·06 to 0·3 grm.

Action and Uses

Supposed to be one of the most efficacious remedies in the treatment of **hypertension** in doses of 5 grs. three times daily after meals. Sometimes nausea, gastro-intestinal disturbances and nervous irritability may follow its use. Others suffer from diarrhœa, muscular fatigue, motor aphasia, hallucination of sight and hearing, delirium, convulsive twitchings, coma and death. In some cases the symptoms resemble those of iodism. It has not proved a success. The potassium salt causes more distressing nausea and weakness. If the patient does not show any satisfactory improvement after 5 gr. doses, taken for two months, the drug will have no effect.

SODII THIOSULPHAS, U.S.P.

Sodium Thiosulphate. (*Not official*)

Characters.—Colourless, odourless, transparent monoclinic prisms. Freely oluble in water.

Dose. U.S.P.—1 grm. or 15 grs., by mouth or intravenously,

Action and Uses

It is largely used as a reducing agent in photography under the name of "Hypo," and has been used in the form of a lotion (1 in 10) as a **parasiticide** in various skin affections, *e.g.*, eczema, furunculosis, urticaria, etc., and internally as a **purgative.** Now-a-days it is used intravenously in **exfoliative dermatitis**, specially those appearing after the use of organic arsenic preparations. It

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is also used against other manifestations of arsenic poisoning. The usual method is to give it intravenously in doses of 0.3, 0.45, and 0.6 grm. in 5 c.c. of distilled water every second or third day. It may be administered in 15 gr. doses by the mouth dissolved in normal saline. It has been recommended in mercurial and bismuth stomatitis and is useful in all acute poisoning from metals. Large intravenous injections aggravate the condition. It acts by dissolving the storage depots and helping elimination by the kidneys, but when a large dose is used a large quantity is suddenly dissolved out which the kidneys cannot eliminate so that it actually increases the poisoning.

AMMONIUM

Ammonia. (*Not official*)

Ammonia preparations may be grouped into two classes, (*a*) those that liberate irritating ammonia from their compounds, and whose action therefore depends upon free ammonia; (*b*) those forming salts homologous with alkali metals, and which act as salts in the body.

1. Preparations whose actions depend upon free ammonia

LIQUOR AMMONIAE FORTIS

Strong Solution of Ammonia. NH_3

Source.—Obtained by heating a mixture of ammonium chloride and slaked lime, and passing the gas (ammonia) into distilled water. Contains 32·5 p.c. of w/w ammonia.

Characters.—A clear, colourless, alkaline liquid; odour, characteristic; very pungent. Sp. gr. 0·885 to 0·891.

Incompatibles.—Acids and acid salts, metallic salts and alkaloids.

Official Preparations

1. **Liquor Ammoniæ Dilutus.** *Syn.—Liquor Ammoniæ; Ammonia Solution.*—10 p.c. w/w of ammonia. **B. P. Dose.—10 to 20 ms. or 0·6 to 1·2 mils.**
2. **Linimentum Camphoræ Ammoniatum.**—25 p.c.
3. **Spiritus Ammoniæ Aromaticus.**—*See* Ammonium Carbonate, page 87.

Pharmacology

Locally.—A solution of ammonia when rubbed in or applied to the skin stimulates the peripheral nerves and superficial blood-vessels, producing a sensation of heat and redness. If it is concentrated and evaporation prevented it blisters. Ammonia is therefore a **rubefacient** and **vesicant.**

Nose and air-passages.—The vapour of ammonia powerfully **irritates** the mucous membrane of the nose and air-passages causing sneezing. It also irritates the conjunctiva producing lachrymation. By exciting the nasal afferent nerves, it **reflexly stimulates circulation,** and accelerates pulse rate. If the inhalation is prolonged, or the vapour is too concentrated, inflammation of the nasal and air-passages results.

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Internally.—On reaching the stomach, ammonia at once **reflexly stimulates the heart and circulation** by its action on the accelerator centre. Like other alkalies it neutralises the acidity of the gastric juice if given during digestion, with the formation of ammonium chloride. It also increases peristalsis and causes a sense of warmth in the stomach. Therefore, it is an **antacid, gastric stimulant** and **carminative.** In large doses, it is a **gastro-intestinal irritant.**

Absorption.—Although ammonia is readily absorbed from the alimentary canal it does not produce any special physiological effect when administered through this channel. If not converted into a chloride by the acid in the stomach it appears in the portal blood as carbonate or carbamate, and carried to the liver where it is converted into urea. The liver is therefore an important factor in the disposal of ammonia, and if the organ is functionating properly, it can prevent the passage of ammonia to the systemic circulation. The systemic effects are only observed after subcutaneous or intravenous administration. The characteristic action of ammonia base is first stimulation followed by paralysis of the central nervous system, specially the medulla. On the cord its effect resembles strychnine and causes reflex irritability followed by convulsion; while it paralyses the motor nerve-endings like curara.

Blood.—Since ammonia is converted into urea in the blood its action differs from the fixed alkalies in not increasing the available alkalinity of the blood.

Heart and circulation.—The immediate result of the reflex effect is vaso-constriction and stimultation of the accelerator centres followed by a rise of blood pressure and stimulation of the heart. But owing to the rapid change of the drug in the system this is of momentary duration.

Lungs.—Respiration is increased by direct stimulation of the **respiratory centre** after absorption. The carbonate is largely used in cough mixtures as it renders the mucus of respiratory tract more fluid. As it is not excreted by the bronchial mucus or by the lungs, its expectorant action is due to the fact that unchanged carbonate of ammonia acts as a nauseant to the stomach and thereby increases the bronchial secretion by reflexly exciting the vagus supplying the mucus glands.

Nervous system.—Ammonia is a **general stimulant,** and by its action on the medulla, it stimulates respiration, constricts the peripheral arterioles, and raises the blood-pressure. These effects are reflex from surface irritation, for they are almost instantaneous and manifest themselves before the drug can be absorbed. In toxic doses, it produces convulsions, due to the stimulation of the motor cells in the cord.

Kidneys.—Ammonia and its salts are changed into urea in

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the liver. They differ from the fixed alkalies in not increasing the alkalinity of the blood and having no effect on the urine except to increase the urea and thus causing some **diuresis.**

Elimination.—Ammonia is thrown off with the breath, sweat, urine and bronchial secretion.

Toxic action.—If a large dose of a concentrated solution be swallowed, it may cause death within a few minutes from suffocation due to spasm of the glottis. Otherwise the symptoms are those of poisoning by a corrosive alkali.

Antidotes.—The same as those of the other alkalies.

THERAPEUTICS

Externally.—As a *local stimulant* to nerve and blood-vessels, the liniment of ammonia is rubbed over **stiff joints,** and in various conditions of **chronic rheumatism** ; and as a *counter-irritant* on the chest in **bronchitis, pneumonia** and **pleurisy.** Ammonia may be used as a *vesicant* in cases where cantharidin is contra-indicated. A piece of lint cut slightly larger than the intended blister is moistened with the strong solution and applied and immediately covered over with a watch-glass. Ammonia neutralises the poison of **nettles** and **insect-bites,** and thereby lessens the pain and swelling caused by them.

The vapour (smelling-salts) is used to rouse patients from **fainting, shock, syncope, stupor** and **narcotic poisoning.**

Internally.—Like other alkalies, ammonia may be given in **acid dyspepsia.** Spirit of sal volatile is a useful remedy for **gastric and intestinal cramps**; a few drops with bicarbonate of soda and dill water give relief to **flatulence in infants.** As a general diffusible stimulant, ammonia is extremely serviceable in **syncope, shock, fainting,** and in the low adynamic conditions of **febrile diseases,** *e.g.* **pneumonia, typhoid,** etc. It makes an excellent "pick-me-up," and softens the phlegm in bronchitis and catarrhal pneumonia, but the carbonate is better. Ammonia controls *iodism,* and is therefore combined with iodides when prescribed in large doses.

AMMONII CARBONAS

Ammonium Carbonate

Syn.—Ammonium Sesquicarbonate.

Source.—A variable mixture of ammonium bicarbonate, NH_4HCO_3, and ammonium carbamate, $NH_4NH_2CO_2$; obtained by subliming ammonium sulphate and calcium carbonate.

Characters.—In translucent, crystalline masses; odour ammoniacal; reaction alkaline. Taste, pungent, ammoniacal. Effloresces when exposed to air. Partially volatilises and is converted into porous lumps or a white powder. *Solubility.*—1 in 4 of water.

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Incompatibles.—Acids, acid salts, lime water, metallic salts, alkaline-earths and alkaloids.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Official Preparations

1. **Liquor Ammonii Acetatis Fortis,** *see* page 90.
2. **Spiritus Ammoniæ Aromaticus.** *Syn.—Spirit of Sal Volatile.*—Contains 21 to 24 p.c. w/v of ammonia. **B.P. Dose.—15 to 60 ms. or 1 to 4 mils.**

AMMONII BICARBONAS

Ammonium Bicarbonate

Source.—May be prepared by passing carbon dioxide into solution of ammonia. Contains not less than 98 p.c. and not more than the equivalent of 102 p.c. of ammonium bicarbonate.

Characters.—White crystals, or fine, white crystalline powder. Taste, pungent, odour ammoniacal. Slightly hygroscopic. Volatilises slowly at ordinary temperature. *Soluble* in 5¼ parts of water; insoluble in alcohol (90 p.c.).

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Pharmacology and Therapeutics

Internally.—The carbonate and the bicarbonate possess all the virtues of the liquor, and in addition are **powerful expectorants,** facilitating the expulsion of viscid mucus. They are therefore very useful in **bronchitis,** and **catarrhal pneumonia.** Given in large doses, or even in small repeated doses, over a long period, they are irritants to the bowels and may give rise to **diarrhœa.** They should therefore be given with caution in cases complicated with diarrhœa. The carbonate is an emetic in ½ dr. doses, though rarely used for the purpose. In the form of aromatic spirit of ammonia it is used as a mild stomachic in **debility** and **alcoholism,** and as a carminative in **flatulence.**

The carbonate or the spiritus ammoniæ aromaticus should not be prescribed with syr. scillæ which contains acetum scillæ and will give off CO_2 gas. It forms insoluble salts with all metals except the alkalies.

2. Preparations which act as salts in the body

AMMONII CHLORIDUM

Ammonium Chloride. NH_4Cl

Syn.—Sal Ammoniac. **Syn. I.V.**—*Nishadal,* Beng. *Noshadar,* Hind.

Source.—Prepared by neutralising ammonia with hydrochloric acid.

Characters.—White, crystalline, granular powder; odourless. Taste, saline, cooling. *Solubility.*—1 in 3 of water, 1 in 60 of alcohol (90 p.c.).

Incompatibles.—Alkalies and their carbonates, mineral acids; lead and silver salts.

B.P. Dose.—5 to 60 grs. or 0·3 to 4 grms.

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Non-official Preparations

1. **Lotio Ammonii Chloridi.** *Syn.—Lotio Evaporans.*—Ammonium chloride 15 grs.; alcohol (90 p.c.) 1 dr.; water to 1 oz.
2. **Vapour Ammonii Chloridi.**—Obtained by mixing hydrochloric acid and ammonia in a suitable apparatus and purifying through water or moist sponge. A useful inhalation in *bronchitis*, and in affections of the throat and eustachian tube.

Pharmacology and Therapeutics

Since ammonium is converted into urea the systemic action of ammonia base is elicited when the chloride is injected intravenously or subcutaneously. It first stimulates and then paralyses the central nervous system and the medulla; increases the reflex excitability of the cord, and causes convulsions like strychnine. The motor nerve-endings are paralysed in frogs, though no such effect is observed in mammals. During convulsion the respiration is arrested and the blood-pressure rises enormously. Death takes place from asphyxia, but if the animal is kept alive by artificial respiration recovery takes place owing to elimination of the salt.

The rise of blood pressure is due to constriction of the peripheral vessels through the vaso-motor centre, and the heart becomes slow from stimulation of the vagal centre from increased blood pressure.

Externally.—Locally applied, a solution of the chloride has a soothing **refrigerant** effect, and this effect is greatly increased by the addition of alcohol or potassium nitrate. A lotion is therefore used in cases of injury to different parts, such as **sprains, bruises,** etc., as a cooling application, and Lotio Evaporans is used for the purpose. The vapour when inhaled increases the secretion of the mucus from the larynx, pharynx, trachea, bronchi, eustachian tube, etc., and is therefore serviceable in **chronic pharyngitis, laryngitis, bronchitis,** and **otitis media.**

Internally.—It is an irritant and astringent and causes a reflex flow of saliva. From the stomach it is rapidly absorbed and is not converted into urea to the same extent as when the carbonate is used. In herbivora it forms urea and liberates chloride ions to combine with sodium and potassium, forming chlorides and are eliminated as such, thus *reducing the fixed alkalies* of the body giving rise to **acidosis.** This action takes place in man to a less extent. Because it causes acidosis and helps the plasma to hold more calcium in solution it is used in **tetany,** and to counteract **alkalosis.**

In the form of lozenges, when allowed to melt slowly, in the mouth, it acts as a **reflex expectorant.** In moderate doses (10 to 15 grs.), it is a **gastro-intestinal irritant,** particularly to the intestine.

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Liver.—It is used as an **indirect cholagogue** in catarrhal jaundice, and at one time was used in the treatment of threatening abscess of the liver. It is doubtful if it possesses any of these effects.

Lungs.—It makes the secretion of bronchial mucus less viscid and helps expectoration. This effect is partly reflex from irritation of the stomach and partly due to salt action in the bronchioles. It is therefore used as an expectorant in **bronchitis**, both acute and chronic.

Kidneys.—It is a **diuretic**, due partly to urea and partly to the reduction in the amount of salts adsorbed by the tissue proteins, and the salts so liberated increase the non-colloidal constituents of the blood thus reducing the resistance to filtration and act as diuretics. It is used with mercurial diuretics to increase their diuretic effect (*see* Novasurol).

Excretion.—It is partly excreted as such, but a large portion as urea.

LIQUOR AMMONII ACETATIS FORTIS

Strong Solution of Ammonium Acetate

Source.—Contains glacial acetic acid 453 G., ammonium carbonate 330 G., strong solution of ammonia 100 mils or q.s., water sufficient to produce 1000 mils.

Characters.—A thin, syrupy liquid with an odour of ammonia and of acetic acid. Sp. gr. 1·098.

B.P. Dose.—15 to 60 ms. or 1 to 4 mils.

Official Preparation

1. **Liquor Ammonii Acetatis Dilutus.** *Syn.—Liquor Ammonii Acetatis; Minderer's Solution.*—12.5 p.c. of strong solution of acetate.

B.P. Dose.—½ to 1 oz. or 8 to 30 mils.

Non-official Preparation

1. **Liquor Ammonii Citratis Dilutus.**—Ammonium carbonate 87·5 G., citric acid 125 G., water to 1000 mils. *Dose.*—2 to 6 drs. or 8 to 24 mils.

Pharmacology and Therapeutics

The solutions of the acetate and citrate are **diaphoretics and diuretics.** The diaphoresis is due to their effect on the sweat centre. If the patient is kept cool, their action concentrates upon the kidneys and there is diuresis. The diuresis is due to the formation of urea in which form they are eliminated. For these actions, they are used as mild, non-depressant **antipyretics in fevers.**

LITHII CARBONAS

Lithium Carbonate. (Not official)

Source.—Obtained from native silicates of lithium.

Characters.—In white powder, or minute crystalline grains. Taste slightly alkaline. *Solubility.*—1 in 80 of water, insoluble in alcohol (90 p.c.).

Dose.—2 to 10 grs. or 0·12 to 0·6 grm.

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LITHII CITRAS

Lithium Citrate. (Not official)

Source.—Prepared by the interaction of nitric acid and lithium carbonate.
Characters.—A white crystalline deliquescent salt. Taste, saline, cooling.
Solubility.—1 in 2 of water.
Dose.—5 to 10 grs. or 0·3 to 0·6 grm.

Pharmacology

Internally.—Lithium salts are readily absorbed and resemble the corresponding potassium salts in their actions, and render the urine alkaline acting like other fixed alkalies. They are powerful gastro-intestinal irritants when used in a concentrated form or in large doses, or even when given subcutaneously. They are diuretics, acting chiefly by salt action, and it was claimed that their prolonged use would dissolve uric acid calculi. But lithium acts as a solvent for uric acid only when present in relatively large amounts, since the quadriurate is not rendered soluble by any lithium salt except in concentrations which would be toxic to man. Moreover, there is no evidence, clinical or otherwise, to show that lithium is more valuable than potassium. These salts are rarely used now.

CALCII CARBONAS

Calcium Carbonate. $CaCO_3$

Syn.—Precipitated Chalk. **Syn. I. V.**—*Khari*, Beng.
Source.—Obtained by the interaction of a soluble calcium salt and a soluble carbonate.
Characters.—A white micro-crystalline powder, insoluble in water. Odourless and tasteless.
Incompatibles.—Acids and acid salts.
B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

CRETA

Chalk. $CaCO_3$

Syn.—Creta Præparata.
Source.—Native calcium carbonate purified by elutriation.
Characters.—White, friable masses, or a white powder. No odour or taste.
Incompatibles.—Acids and sulphates.
B.P. Dose.—15 to 60 grs. or 1 to 4 grms.
Enters into.—Hyd. c. Creta, and the

Official Preparations

1. **Pulvis Cretæ Aromaticus.**—25 p.c. B.P. Dose.—10 to 60 grs. or 0·6 to 4 grms.
2. **Pulvis Cretæ Aromaticus cum Opio.**—2·5 p.c. opium or $\frac{1}{7}$ gr. morphine in 60 grs. B.P. Dose.—10 to 60 grs. or 0·6 to 4 grms.

Non-official Preparations

1. **Mistura Cretæ Co., B. P. C.**—Pulv. Cretæ Arom. 180 grs., Chalk 180 grs., Sp. Ammon. Arom. 180 ms., Tr. Catechu 1¼ oz., Tr. Card. Co. 360 ms., Tr. Opii 60 ms., Sucrose 1 oz., Tragacanth Powder 40 grs., Cinnamon Water to 20 oz. *Dose.*—1 oz. or 30 mils.
2. **Mistura Cretæ.** *Syn.—Chalk Mixture.*—Prepared chalk 30 G., tragacanth powder 5 G., sucrose 60 G., cinnamon water q. s. to 1000 mils. *Dose.*—½ to 1 oz. or 15 to 30 mils.

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Pharmacology

Locally chalk is a mild **astringent** and **desiccant.**

Internally. **Alimentary canal.**—Chalk acts as a direct local **antacid,** neutralising free acids in the mouth and stomach. If not already acted upon, it passes readily into the intestine, where it acts as an **antacid** and a non-irritating **astringent,** caused by (1) the neutralisation of any acid it meets, with formation of chloride or lactate and thus reducing the secretion; (2) formation of a protective coating over the intestinal mucous membrane which also diminishes reflex peristalsis; (3) adsorption of toxins; and (4) depressant action on the intestinal canal due to calcium ion. Lime salts are feebly absorbed on account of their low diffusive power and are excreted with the fæces.

Kidneys.—Some think that calcium carbonate is a **diuretic** because certain mineral waters, such as Contrexeville and Vittel containing calcium bicarbonate and sulphate, among other salts, have been found useful solvents for **uric acid.** But there is no direct evidence.

Therapeutics

Externally.—Chalk may be used as a dusting powder in **excoriations, burns** and **weeping eczema.** Duckworth uses it in the form of an ointment (1 in 1 of benzoinated lard) in **erysipelas.**

Internally. **Alimentary tract.**—Chalk is used as a basis for almost all the tooth powders. As an *antacid* it may be used in **acid dyspepsia,** but lime water acts much better. Aromatic chalk powder is an excellent remedy for mild **diarrhœa,** especially that of children with sour-smelling stools. If the diarrhœa is caused by some irritating food, a dose of castor oil should precede its use. In diarrhœa chalk acts like bismuth salts by forming an insoluble coating over the mucous membrane. Lime salts are of special value in **acid poisoning,** especially in oxalic acid poisoning, as they form insoluble oxalates.

Prescribing hints.—Generally given in the form of chalk mixture with opium and astringent tinctures. Aromatic chalk powder with bismuth and grey powder is very useful in *infantile diarrhœa.*

CALCII CHLORIDUM

Calcium Chloride. $CaCl_2$

Source.—Formed by neutralising hydrochloric acid with calcium carbonate, evaporating the solution, and desiccating at a temperature not exceeding 200°C.

Characters.—In dry, white granules or porous deliquescent masses. Taste, warm, slightly bitter. *Solubility.*—1 in 1·5 of water, 1 in 3 of alcohol (90 p.c.).

Incompatibles.—Carbonates, phosphates, sulphates, and tartrates.

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B.P. Dose.—10 to 30 grs. or 0·6 to 2 grm. *Intramuscular.*—½ to 1½ grs. or 0·03 to 0.1 grm. *Intravenous.*—5 to 15 grs. or 0.3 to 1 grm.

CALCII LACTAS

Calcium Lactate. $Ca(C_3H_5O_3)_2,5H_2O$

Source.—Obtained by neutralising dilute lactic acid with calcium carbonate and evaporating the resulting solution.

Characters.—A white, almost tasteless powder. *Soluble* in 18.5 parts of water. Readily soluble in hot water. Forms a clear colourless solution.

B.P. Dose.—15 to 60 grs. or 1 to 4 grm.

Non-official Preparations

1. **Syrupus Calcii Lactophosphatis.**—Calcium lactate 75 grm., concentrated phosphoric acid 45 mils., sugar 700 grm., commercial orange flower water 25 mils., water q.s. to 1000 mils. *Dose.*—30 to 60 ms. or 2 to 4 mils.

2. **Calcii Gluconas.**—9.3 p.c. of calcium. Almost tasteless. Given subcutaneously does not produce irritation or necrosis of the tissues. Intravenously, toxicity one-fourth of chloride. *Dose.*—3 to 5 G. three times a day after meals. 1 G. (in 10 p.c. solution) on alternate days *intramuscularly.*

3. **Calcii et Sodii Lactas, B.P.C.**—Occurs as white powder or as colourless, hard granules. Deliquescent. Soluble in 15 parts of water. Action same as other calcium salts, but is more soluble and easy of absorption. Specially useful in *night sweats of phthisis, hæmoptysis* and *difficult dentition*, and in certain types of *dermatitis. Dose.*—0.3 to 2 grm. or 5 to 30 grs.

CALCII PHOSPHAS

Calcium Phosphate. $Ca_3(PO_4)_2$

Source.—Obtained by the interaction of calcium chloride and sodium phosphate in the presence of ammonia.

Characters.—A light, white, amorphous powder. No odour or taste.

Solubility.—Insoluble in water.

B.P. Dose.—10 to 30 grs. or 0·6 to 2 grm.

Pharmacology and Therapeutics

Calcium is an important constituent of the animal body, and it is to the large proportion of calcium phosphate which it contains that the body skeleton owes its most essential property of rigidity. It is present to a considerable amount in all soft tissues and the blood, and is essential to most forms of living matter, and for the activity of certain ferments. Thus the milk will not curdle, nor the blood will coagulate, in the absence of calcium. Important as it is to the body mechanism, provision is made for its supply, and calcium is present in both animal and vegetable foods, although vegetable foods are much richer in calcium than the foods of animal origin. Milk and yolk of eggs are specially rich in calcium in a readily assimilable form. The young animal therefore is freely supplied with calcium at a period of life when it is necessary for its growth. Deficiency of calcium in food, therefore, has a prejudicial effect on the growing animals,

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owing to the larger amount of calcium necessary for the growth of the skeleton during this period, although very little untoward effect is observed in grown up animals.

The changes following calcium starvation resemble those observed in rickets in children. In rickets, however, the softness of the bones is not due to any deficiency of calcium in the food, but to lack of sunlight and vitamin D, which promote the absorption of calcium and phosphorus in balanced proportion, so that lime is not deposited on the bones.

Another condition which resembles rickets of children is sometimes observed in women during the period of pregnancy and lactation. Owing to the excessive demand of the growing child, the mother's skeleton becomes depleted of calcium which becomes soft and spongy, unless this demand is met by proper supply of calcium. This condition is known as osteomalacia, and like rickets is due to deficiency of vitamin D, lack of sunlight and derangement of calcium metabolism.

Calcium is present in all tissues, and not only the heart but other tissues of the body are sensitive to disturbances in the amount of calcium and sodium in the blood. Given intravenously in large doses, lime salts lessen the irritability of the cerebral cortex, while deficiency of the calcium in the blood causes increased irritability of the brain with muscular twitchings.

An intravenous injection of chloride in non-toxic doses in man is followed by flushing of the skin and face, a hot feeling over the whole body, constriction of the throat, and sometimes nausea and vomiting. The peripheral vessels dilate and the systolic pressure falls. The heart becomes **slow from vagus stimulation** which is antagonised by atropine, the action resembling digitalis in some respects. Soon, however, the rate becomes normal and even accelerated, and the blood pressure rises from stimulation of the sympathetic.

On isolated heart calcium antagonises the depressant effect of potassium, and its absence stops rhythmic activity of other plain and striated muscles which reappears with increased tone on the addition of calcium. In cases of weakness of the cardiac muscle caused either by valvular insufficiency or myocarditis, the addition of chloride to the digitalis treatment increases the optimum action of the latter.

The **pupils** are **contracted** from direct stimulation of the sphincter, and probably from partial stimulation of the nerve ending. This is followed by **dilatation** from sympathetic stimulation.

All the above effects are elicited by the intravenous injection, and are not so marked when administered by the mouth, due to slow absorption. Calcium antagonises the effect of magnesium and potassium.

The normal calcium requirement of an adult is about 0·45

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grm. daily. During the growing period, pregnancy and period of lactation the demand is greater. It is absorbed with difficulty, and it has been estimated that only 60 p.c. of calcium of the food is absorbed. Therefore 1 grm. of calcium must be taken daily with food to supply the adequate requirement. One litre of fresh cow's milk contains 1 grm. of calcium.

Whether given in soluble or insoluble form, calcium is absorbed with difficulty. Its absorption depends upon the nature of the intestinal contents. During the digestive period the reaction of the upper part of the gut is frequently on the acid side and absorption of calcium takes place in the form of acid calcium phosphate. If the contents of the intestine be alkaline, calcium is precipitated as insoluble carbonate or phosphate, and deficiency of vitamin D renders the gut contents more alkaline and therefore retards absorption. If the intestine contains unsaturated fatty acids as derived from codliver oil, butter or bacon fat, calcium forms soluble soap and is readily absorbed. Calcium salts of fatty acids though insoluble are absorbed as soluble calcium salts possibly due to their solubility in bile. Calcium metabolism is regulated by ultra-violet rays, and Fusshall (*American Journal of Physiology*, 1928) has shown that on a less calcium diet, as compared to controls, irradiated rats showed distinctly better calcium deposition, growth and increased calcium content of the serum.

Calcium is essential to the process of normal coagulation of the blood, which may be prevented by precipitating this salt by oxalates, citrates, and fluorides. It is also necessary for the action of thrombokinase or for the conversion of prothrombin into thrombin. Administered *per os* these salts have no appreciable effect in increasing the calcium content of the blood. Given intravenously or subcutaneously, the calcium content of the blood may remain high for a short time, the strength and duration depending not only upon the amount of calcium given but also on the calcium content of the blood. It is, however, used in **purpura, aneurism, hæmophilia, hæmoptysis** and other **internal hæmorrhages,** and as a preventive before operation in persons suffering from jaundice, or subject to hæmorrhage.

Calcium circulates in the blood partly in combination with proteins and partly as diffusible salt. Of the diffusible calcium the portion existing in an ionised form performs the important functions. The normal blood serum contains 9 to 11 mg. of calcium per 100 c.c. and this concentration is constant, and is regulated by the parathyroid hormone, calcium in the food, reaction of the tissues, and vitamin D. In tetany following parathyroidectomy the calcium content of the blood is diminished, sometimes falling as low as 5 mgrm. per 100 c.c., and the symptoms following parathyroidectomy or of tetany may be checked by restoring the blood calcium

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level to normal by the use of large doses of calcium, or by the injection of parathyroid hormone, or by measures which increase the acid balance of the body, *e.g.*, acids, ammonium chloride or calcium chloride, which cause acidosis. It has been shown that the acid-balance determines the concentration to which the plasma can hold calcium in solution. Conversely any change in the reaction of the blood towards alkalinity decreases the amount of *functioning* diffusible calcium without altering the calcium content. In tetany and spasmophilia of children following rickets, good results are obtained by the use of large doses of calcium which **depress nervous excitability**. The chief point is to cure rickets when the symptoms of spasmophilia will disappear. Since parathyroid increases the serum calcium at the expense of the calcium of the bones, which are already deficient, the use of parathyroid is contra-indicated in rickets (*see* Parathyroid).

The soluble lime salts increase the resistance of the red blood cells to certain hæmolytic serums and also lessen the liability to **anaphylactic reaction** in sensitive persons. They are of great value in **bronchial asthma** where they increase the sympathetic excitability in cases with evidence of vagotonia; and are also useful in **hay fever, acute rhinitis, serum disease,** and other conditions attended with parasympathetic excitability. It is used in **pleural effusions** on the hypothesis that there is a disturbance of the calcium-sodium balance in the tissues, there being a comparative deficiency of the former and corresponding increase of the latter.

Owing to the constant demand on the part of the growing fœtus for calcium, the serum calcium of the mother becomes low, and administration of calcium during pregnancy and the period of lactation protects the mother from calcium deficiency by maintaining the calcium at its proper level.

It is largely used nowadays in **pulmonary tuberculosis** on the assumption that the healing of tubercular lesions in the lungs is associated with calcification and that there is excessive excretion of calcium in this disease. There is however no reason to believe that there is any deficiency of serum calcium in this disease, and clinical results are not unanimous. In a certain number of cases a temporary benefit is observed as it reduces the temperature, improves the appetite, checks night sweats, and helps the patient to gain in weight. In intestinal tuberculosis it is used with better results in early cases, but is of no use in severe forms, although it is worthy of a trial. Owing to the deficiency of calcium, its use has been suggested in **sprue** either alone or with parathyroid.

Calcium is useful in **lead poisoning** as it causes elimination of lead from the body by increasing the exchange of calcium and lead between the bones and the blood. During acute attacks it helps storage of lead in the bones and the lactate is

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given in 30 gr. doses three times a day, or a 5 p.c. solution of chloride intravenously. After the acute stage, slowly mobilise the stored lead by low calcium intake and by producing acidosis. Administration of calcium prevents damage to the liver caused by carbon tetrachloride.

One of the important specific actions of calcium is its power to retard inflammatory process, and that transudation and œdema are favoured by withdrawal of calcium, which normally serves to check the permeability of the vessels. Calcium is therefore used in **serous headaches, angioneurotic œdema, chilblains,** and conditions suggesting abnormal permeability of vessels, but the results have been disappointing.

The chloride increases the acidity of the urine, as quite a large part of calcium is converted into carbonate and escapes absorption, the liberated chloride is absorbed and increases the proportion of fixed acids in the body causing acidosis. It is a powerful **diuretic** due to increase of non-colloidal constituents of the blood. It has been used in **acute** and **subacute nephritis** where it helps the elimination of chlorides.

To promote **nutrition** and **cell growth,** the phosphate is exceedingly useful in the case of children who have overgrown their strength; women weakened by child bearing, prolonged suckling, or excessive menstruation ; anæmia and exhaustion brought about by prolonged suppuration, diarrhœa, leucorrhœa, etc.

The phosphate is also used to expedite the union of fractures and the healing of caries of bones. It is also useful for those who have overworked their strength.

Excretion of calcium takes place through the intestine mainly (about 75 p.c.) and less with the urine, depending upon whether it forms a soluble or insoluble salt in the intestine. If it forms an insoluble phosphate it is excreted with the stool, whereas if it forms a soluble chloride it is mainly excreted with the urine.

Prescribing hints.—Calcium is best given in solution after food. But as all lime salts are feebly absorbed we are doubtful as to the wisdom of giving them in excessive doses as they may derange the stomach. The objection to the use of chloride is the taste. But this is noticed only when concentrated solutions are used. For the treatment of tuberculosis it is given intravenously for prolonged periods in 5 to 10 p.c. solutions ; commencing with 2 c.c. and then working up to 10 c.c. Given subcutaneously, or when it leaks into the tissues during intravenous administration, local inflammation and necrosis result. For its diuretic effect the chloride is given in large doses (30 to 40 grs.), three or four times a day. Given intravenously the effects are quicker and more definite than oral administration. In urgent cases therefore it should be given intravenously in doses of 0.25 grm. in 5 c.c. of water.

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Subcutaneous injections of chloride may cause sloughing, but gluconate does not. Ordinarily intramuscular injection gives just as good results and the gluconate is used for the purpose. The action of the lactate is somewhat weaker and therefore larger doses are required; it may be used either in the form of powder or as tablets. Calcium should not be prescribed with carbonates, sulphates, or spt. ammon. aromat. which will throw insoluble precipitates.

CALCII HYDROXIDUM

Calcium Hydroxide. $Ca(HO)_2$

Syn.—Calcii Hydras; Slaked Lime. **Syn. I. V.**—*Chun*, Beng. *Chunam*, Hind.

Source.—Freshly prepared by the action of water on lime.

Characters.—A white alkaline powder. *Solubility.*—Slightly soluble in water; more freely in solutions of glycerin and of sugars.

Incompatibles.—Vegetable and mineral acids, and metallic salts.

B.P. Dose.—5 to 15 grs. or 0·3 to 1 grm.

Official Preparation

1. **Liquor Calcii Hydroxidi.** *Syn.—Liquor Calcis; Lime Water.*—0·15 p.c. w/v of calcium hydroxide. A clear, colourless liquid with alkaline taste. Absorbs CO_2 from the air and forms a film of calcium carbonate on the surface. **B.P. Dose.—1 to 4 oz. or 30 120 mils.**

Pharmacology

Externally.—Unslaked or slaked lime is a **caustic**, but its action is localised. Lime water is a local **sedative** and **astringent** when applied to the broken skin.

Internally. **Alimentary canal.**—The chief action of the oxide and hydroxide is due to the alkalinity and not to the calcium. Like chalk, lime water neutralises free acids of the contents of the stomach and acts as an **antacid**, but more powerfully. It makes the curd of milk more flocculent. It has a slight **sedative** property. In the intestine it is an **antidote** for poisoning by mineral acids, oxalic acid and zinc chloride.

Therapeutics

Externally.—As a *caustic* in the form of Vienna Paste (*see* page 67), slaked lime may be used to destroy **warts** and small **epithelial** and other **growths.** Lime water, either with linseed oil (Carron oil), olive oil or glycerin, is a soothing application to **burns** and **scalds.** An addition of 1 to 2 p.c. of phenol increases its efficacy. It makes a soothing astringent dressing for weeping **eczema,** and may be used as an injection to lessen the discharges in **leucorrhœa, gonorrhœa, gleet, otorrhœa,** etc., even when inflammation is present.

Internally. **Alimentary tract.**—It is chiefly used as a diluent for milk to make the curd more flocculent (1 in 3 or

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more), and to check **vomiting** of infants. In the same way it may be given in **enteric diarrhœa** and other affections to prevent the milk from forming hard indigestible lumps, but its use has now been replaced by sodium citrate. As an astringent it is useful in mild **intantile diarrhœa.**

Prescribing hints.—Lime water is ordinarily given in milk. To suckling babies one teaspoonful with an equal quantity of milk may be given every 3 hours before nursing, and to hand-fed ones a dessert-spoonful in each bottle.

MAGNESII OXIDUM LEVE

Light Magnesium Oxide

Syn.—Magnesia Levis; Light Magnesia.

Source.—Prepared by heating light magnesium carbonate to a dull red heat.

Characters.—A very light, white powder; odourless; taste slightly alkaline. Almost insoluble in water.

B.P. Dose.—10 to 60 grs. or 0·6 to 4 grms.

OFFICIAL PREPARATION

1. **Mistura Magnesii Hydroxidi.** *Syn.—Cream of Magnesia.*—Contains 8·25 p.c. w/v of magnesium hydroxide, or 12.5 grs. in 240 ms. **B.P. Dose.—60 to 240 ms. or 4 to 16 mils.**

MAGNESII OXIDUM PONDEROSUM

Heavy Magnesium Oxide

Syn.—Magnesia Ponderosa; Heavy Magnesia.

Source.—Prepared by heating heavy magnesium carbonate to a dull red heat.

Characters.—A white powder; almost insoluble in water, but readily dissolved by acids. Insoluble in alcohol (90 p.c.). Odourless; taste, slightly alkaline.

Incompatibles.—All acids.

B.P. Dose.—10 to 60 grs. or 0·6 to 4 grms.

MAGNESII CARBONAS LEVIS

Light Magnesium Carbonate

Source.—Prepared by boiling together *dilute* solutions of magnesium sulphate and sodium carbonate.

Characters.—A light, white powder consisting of amorphous particles and slender prisms. Odourless; almost tasteless. *Solubility.*—Almost *insoluble* in water, insoluble in alcohol (90 p.c.). Soluble in dilute acids with effervescence.

B.P. Dose.—10 to 60 grs. or 0·6 to 4 grms.

Enters into.—Pulv. rhei co.

MAGNESII CARBONAS PONDEROSUS

Heavy Magnesium Carbonate

Source.—Prepared by mixing boiling concentrated solutions of magnesium sulphate and sodium carbonate, evaporating to dryness, and washing the product.

Characters.—A white, granular powder; odourless and tasteless. Almost *insoluble* in water, and in alcohol (90 p.c.); soluble with effervescence in dilute acids.

B.P. Dose.—10 to 60 grs. or 0·6 to 4 grms.

Enters into.—Pulv. rhei co., Troch. bismuthi co.

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Official Preparation

1. **Liquor Magnesii Bicarbonatis.** *Syn.—Fluid Magnesia.*—7½ grs. in 1 oz. A clear, colourless liquid, may effervesce when the bottle is first opened. **B.P. Dose.—1 to 2 ozs. or 30 to 60 mils.**

Non-official Preparations

1. **Mistura Alba, B.P.C.**—Light Mag. Carb. 400 grs., Mag. Sulph. 5 ozs., Peppermint Water 20 ozs. *Dose.*—½ to 1 oz. or 15 to 30 mils. as an aperient.
2. **Liquor Magnesii Citratis, U.S.P.** *Syn.—Lemonade Purgative.*—Magnesium Carbonate 15, Acid Citric 35, Syrup 60, Ol. Lemon 0.1, Talc 5, Pot. Bicarb. 2.5, Water to 350. A pleasant refrigerant draught and saline aperient. *Dose. U.S.P.*—350 c.c. or 12 oz.
3. **Red Mixture** (Dr. Goodeve's).—Mag. Carb. Pond. 30 grs., Rhubarb 10 grs., Spt. Ammon. Aromat. 30 ms., Ol. Anisi 2 drops, Water to 2 ozs. Mix. *Dose.*—One teaspoonful every 3 or 4 hours till bowels operate.

MAGNESII SULPHAS

Magnesium Sulphate. $MgSO_4,7H_2O$

Syn.—Epsom Salts.

Source.—Prepared by the interaction of magnesium carbonate and sulphuric acid. Contains 99·5 to 102 p.c. of pure magnesium sulphate.

Characters.—Colourless crystals; odourless. Taste, cool saline and bitter. Effloresces in dry air. *Soluble* in 1.5 parts of water, sparingly soluble in alcohol (90 p.c.).

Incompatibles.—Potassium and sodium carbonates and bicarbonates, lime water, lead acetate, and tartarated soda which precipitates magnesium tartrate.

B.P. Dose.—30 to 240 grs. or 2 to 16 grms.

Enters into.—Mist. sennæ co. and mist. magnesii hydrox.

Pharmacology of Magnesium Salts

Internally. **Gastro-intestinal canal.**—Both the oxide and the carbonate are **alkaline,** and neturalise the normal or the excessive acidity of the stomach, and the oxide does this without inducing subsequent hypersecretion. They act as antacids. Being sparingly soluble their antacid action extends down the intestine, where they are converted into soluble and therefore cathartic magnesium bicarbonate. What is unaffected is left insoluble. The carbonate sets free carbonic acid, which exerts a local sedative influence and provokes subsequent hyperacidity. (For action of Magnesium Sulphate, *see* Purgatives).

Blood.—Magnesium salts enter the blood as a chloride or lactate and render the **plasma more alkaline.** If salines are used in concentrated form they draw fluid from the blood and tissues and render the blood more concentrated.

Nervous system.—Taken by the mouth, magnesium salts have very little systemic effect owing to thier slow absorption and rapid elimination. The typical effects of Mg-ion are elicited when the salts are given either intravenously or subcutaneously. Magnesium acts as a **narcotic** and **anæsthetic** resembling chloroform, but unlike other hypnotics, it

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acts *indifferently* upon all parts of the central nervous system. The heart is little influenced, the vagus remaining unaffected. Magnesium depresses the central and peripheral nervous system, and death takes place from paralysis of respiration. It reduces the irritability of the intestine and counteracts the effect of physostigmine and barium. On the voluntary muscles it acts like curare. Injected into the spinal canal (5 c.c. of a 12 p.c. solution), or applied to the nerve trunks (25 p.c.), the sulphate induces anæsthesia resembling cocaine, but more lasting. All these symptoms are antagonised by the use of calcium salts intravenously, which restore the equilibrium between the various ions disturbed by an excess of magnesium.

Urine.—What little salt is absorbed is passed out by the kidneys, **increasing the flow of urine**, rendering it **alkaline**, and to a certain extent **dissolving uric acid**; but the diuretic effect is weaker than that of the potassium and sodium salts. When given parenterally it is mostly excreted by the kidneys, almost the entire amount being eliminated within 48 hours.

Therapeutics

Externally.—A saturated solution of magnesium sulphate used as a compress relieves pain and acts as a local anæsthetic and has been used in **erysipelas, orchitis, arthritis** and other **inflammatory affections.** Morrison recommends dressing of wounds with **Magnesium Sulphate Paste** made by mixing in a warm mortar dry magnesium sulphate 1½ lbs., and 11 ounces of glycerole of carbolic acid (1 in 10). The dressing is left unchanged for three to eight days when profuse discharge of serum takes place, when more wool is used; subsequently a solution of the sulphate is used. This acts by osmosis and draws fluid from the wound and prevents growth of aerobic and anaerobic organisms.

Internally.—The oxide and the carbonate are largely employed in **acid dyspepsia, heartburn, pyrosis, vomiting, sick headache,** or any other complaint attended with acidity. Their antacid property is considerably increased by combining them with sodium bicarbonate and bismuth carbonate, as in the treatment of **hyperacidity, gastric** and **duodenal ulcer** and **chronic gastric catarrh.** In all these conditions it should be given on an empty stomach in order that the insoluble salts may form a protective coating over the gastric mucosa and neutralise hyperacidity. As a tasteless, unirritating alkaline laxative, they are often used in combination with rhubarb, as pulv. rhei co., and Goodeve's "Red Mixture" in **constipation of children.** Liq. magnesii bicarbonatis, is an agreeable and alkaline laxative in acid dyspepsia accompanied by constipation.

As **antidotes,** magnesia and the carbonates are used in **poisoning** by **mineral acids, oxalic acid,** and the salts of

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mercury, arsenic and **copper,** as they form insoluble compounds with them. In **alkaloidal poisoning** they hinder the absorption of alkaloids by making the contents of the stomach alkaline. But in order to get these antidotal effects, they must be given in very large doses, which is the only objection. Magnesium sulphate acts as an **antidote** to **lead** and **barium** salts by precipitating their insoluble sulphates.

As a **diuretic** and feeble alkaliser of blood and urine, they are used in **gout** and **gravel** cases, where the salts of potassium and sodium are not well borne. Many mineral waters containing magnesium are valuable diuretics, such as Harrogate, Carlsbad, Ems, Baden-Baden, etc.

For its paralysing effects on the nerve tissue the sulphate has been used as intraspinal injection in **tetanus** (3 to 4 c.c. of a 25 p.c. solution), and for the production of **spinal anæsthesia.** In tetanus it relieves spasms, but does not cure. Similarly intravenous injections of 10 to 25 mils (150 to 375 ms.) of a 10 p.c. solution have been used to relieve spasms of **eclampsia.** It has also been used hypodermically in **chorea** and **epilepsy** (3 mils of a 7·3 p.c. solution); and to relieve **intracranial pressure,** when concentrated solution has been used per rectum (3 to 6 oz. in water). Because of its hypnotic property, it has been recommended (intramuscularly 0·25 G. per kilo) as a preliminary to ether anæsthesia, when it reduces the minimal concentration of ether required to produce general anæsthesia. As an enema, or intravenously (2 c.c. of a 50 p.c. solution), it is valuable in headaches following spinal anæsthesia. The *margin of safety* between the effective therapeutic dose and the toxic dose being small this restricts its use, as it paralyses the respiratory centre when used in large therapeutic doses.

Note.—For injection the solutions should be sterilised in an autoclave.

BARII SULPHAS

Barium Sulphate. $BaSO_4$

Source.—Prepared by the interaction of a soluble barium salt and a soluble sulphate.

Characters.—A heavy, white, amorphous powder. No odour, or taste. Stable in air. *Insoluble* in water, slightly soluble in hydrochloric acid, and in nitric acid.

Non-official Preparations

1. **Pulvis Barii Sulphatis Compositus, B.P.C.** *Syn.—Barium Meal*; *Shadow Meal.*—Barium sulphate, 750; cocoa powder, 94; arrowroot, 94; compound powder of tragacanth, 31; sucrose in powder, 31. *Dose.*—120 to 240 grm. or 4 to 8 oz.

2. **Barii Chloridum.**—Colourless crystalline plates, soluble in 2½ parts of water. *Dose.*—½ to 1½ grs. or 0.03 to 0.1 grm. Maximum single dose 3 grs.

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Action and Uses of Barium

Barium belongs to the group of alkaline earths but is more poisonous. The soluble salt (chloride) is absorbed with difficulty from the intestine but sufficiently to produce systemic effect. The chief action is exerted on all forms of muscular tissue which are powerfully stimulated. On the skeletal muscles the effects resemble those of veratrine, and since they are not antagonised by curara, it acts directly on the contractile substance. All the plain muscles are similarly affected, *e.g.*, those of the intestine, bladder, vessels, and bronchi. Owing to the vaso-constriction it causes a rise of blood pressure. It increases the excitability of the heart, slows the rate and improves its tone, resembling digitalis effects; and at one time was suggested as a substitute for that drug. In practical therapeutics, however, it has not come up to the expectations made of it, although its use has been suggested in syncope of **heart block.**

Given by the mouth in large doses, the chloride causes nausea, vomiting, colicky pain and severe diarrhœa, tonic and clonic convulsions and death from paralysis of the central nervous system.

Sulphate of barium is insoluble and passes through the body unchanged, and being opaque to X-rays is used in preference to bismuth as a contrast meal in X-ray examination of the alimentary canal, either by the mouth or per rectum. Two to 5 ounces is generally required, and is given mixed with cornflour, kaolin and malted milk, or in the form *shadow meal.* Atropine is a valuable adjuvant specially for visualisation of the appendix, for which object it is given as an enema one hour before barium ($\frac{1}{64}$ gr. or 0.001 G.). Barium however is inferior to bismuth, which, owing to its high molecular weight, gives a darker shadow.

Caution.—As accidental deaths have taken place by the use of poisonous *barium sulphide* when the sulphate has been prescribed, the physician should be careful in writing the prescription in full, without abbreviation, and should satisfy himself before allowing the patient to take the drug. It is always safe to order some special preparation intended for X-ray examination only.

Baryta Sulphurata, B.P.C. *Syn.—Sulphide of Barium.*—It is a caustic and poison, and it is used as a depilatory to remove superfluous hairs mixed with wheat starch in the proportion of 1 to 3. Make a paste with water and apply on the part and scrape off with a blunt knife after five to ten minutes.

GROUP II: ACIDS

Acid Acetic, Trichloracetic, Citric, Tartaric, Hydrochloric, Nitric, Sulphuric, Phosphoric, Hypophosphorous, Lactic, Boric (*see* Antiseptics), Hydrobromic (*see* Bromides).

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ACIDUM ACETICUM

Acetic Acid. $C_2H_4O_2$

Source.—Prepared by the destructive distillation of wood, or by diluting glacial acetic acid.

Characters.—A clear, colourless liquid with a pungent odour. Taste, sharply acid. Sp. gr. 1.044-1.045.

Official Preparations

1. **Acidum Aceticum Dilutum.**—6 p.c. of acetic acid. Sp. gr. 1.008. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**
2. **Oxymel.—15 p.c. B.P. Dose.—30 to 120 ms. or 2 to 8 mils.**

ACIDUM ACETICUM GLACIALE

Glacial Acetic Acid. $CH_3.COOH$

Source.—Obtained by the action of sulphuric acid on an acetate, or by synthesis.

Characters.—A clear, colourless liquid with pungent odour. Miscible with water and most fixed and volatile oils. Sp. gr. 1.055-1.058.

Enters into.—Lint. terebinth. acet.

Pharmacology and Therapeutics

Externally.—Glacial acetic acid is a **caustic** and is therefore used for destroying **corns** and **warts.** It speedily **vesicates,** and may be used in those cases where cantharidin cannot be employed, but it causes much pain, and if not cautiously applied, may produce a nasty sore.

Acetic acid destroys **tinea,** and is an effective application for ring-worm. Vinegar, or diluted acetic acid is an **external refrigerant,** and may be used as a **cooling lotion** in cerebral congestion, sprains and bruises; and sponging with vinegar will **reduce pyrexia** and **check excessive sweating.**

Internally.—Dilute acetic acid allays **thirst** by increasing the salivary secretion, and may be used as a **gargle** (15 ms. to 1 oz.) in cases where dryness of the mouth is a troublesome symptom.

After prolonged use it diminishes the number of red blood-corpuscles and therefore its employment in obesity is contra-indicated. As an internal refrigerant, it may be given in **fevers, cholera, diabetes, Bright's disease,** etc.

Acetic acid is excreted in the urine as a carbonate. Given in large doses it passes out unchanged.

ACIDUM TRICHLORACETICUM

Trichloracetic Acid. $CCl_3.COOH$

Source.—May be prepared by the oxidation of chloral with nitric acid. Contains not less than 98 p. c. of trichloracetic acid.

Characters.—Colourless, very deliquescent crystalline masses with a characteristic pungent odour. *Soluble,* freely in water (9 in 1), in alcohol (90 p.c.), and in ether. Should be kept in well closed containers.

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Pharmacology and Therapeutics

Trichloracetic acid is a caustic, less painful than nitric acid. A weak solution is useful in **stimulating granulating surface** and for washing wounds and ulcers, specially **phagedænic ulcers** of the cheek. As a caustic it is used in warts, and to cauterise venereal and other sores. Mixed with glycerin (1 in 2) it is used in chronic pharyngitis. The pure acid has proved successful in **leiomyoma cutis.** Growths in the bladder have been treated at the University Clinic, Berlin, with a freshly prepared solution applied directly on the surface of the growth by means of a catheter passed through a cystoscope. The solution is made by heating the crystals in a test-tube until they become fluid, and to each 5 c.c. of the solution is added 5 drops of glycerin. 20 to 30 drops being slowly passed through the catheter. To prevent recrystallisation it is placed in a glass of warm water before using. It forms a delicate test for albumin in urine. A few drops of saturated solution added to the urine slowly forms a white cloud at the junction of the two fluids.

ACIDUM CITRICUM

Citric Acid. $C_6H_8O_7,H_2O$

Source.—Obtained from lemon juice, or may be prepared from glucose.

Characters.—Large, colourless crystals, or a white powder; slightly hygroscopic in moist air, and slightly efflorescent in dry air; odourless. Taste, strongly acid. *Soluble* in less than 1 part of water, in 1.5 parts of alcohol (90 p.c.).

20 grs. of Citric Acid in 1 oz. of water } will neutralise { 28·5 grs. of Pot. Bicarb. / 24 grs. of Sod. Bicarb. / 15 grs. of Ammon. Carb.

B.P. Dose.—5 to 30 grs. or 0·3 to 2 grm.

ACIDUM TARTARICUM

Tartaric Acid. $H_2C_4H_4O_6$

Source.—Prepared from potassium acid tartrate. Contains not less than 99·5 p.c. of hydrogen tartrate.

Characters.—Colourless crystals, or a white powder; odourless; taste acid. *Solubility.*—Less than one part of water and in 2·5 parts of alcohol (90 p.c.).

Incompatibles.—Salts of calcium, potassium, lead, mercury, alkalies, carbonates and vegetable astringents.

20 grs. of Tartaric Acid in 1 oz. of water } will neutralise { 27 grs. of Potass. Bicarb. / 22 grs. of Sodium Bicarb. / 15 grs. of Ammon. Carb.

B.P. Dose.—5 to 30 grs. or 0·3 to 2 grm.

Pharmacology and Therapeutics of Citric Acid and Tartaric Acid

Internally.—These acids unite with the bases to form neutral salts, and when given in an effervescing form the

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liberated carbonic acid gas acts as **gastric sedative**, therefore effervescing mixtures are used to check **nausea** and **vomiting**. Because they stimulate salivary secretion, they are used as refrigerant drinks in the form of lemonade to allay thirst in fevers.

Both citric acid and tartaric acid are used in the preparation of effervescing draughts and mixtures.

When added to drawn blood citric acid retards clotting by combining with calcium and forming a non-ionisable salt. Given by the mouth no such effect is observed. They are converted into neutral salts in the stomach and are deoxidised after absorption, *e.g.*, potassium citrate is decomposed into potassium carbonate, carbonic acid and water, thereby increasing the alkalinity of the plasma.

Urine.—They are eliminated as carbonates, thereby increasing the alkalinity of the urine, except when given in large doses when they escape unchanged.

ACIDUM HYDROCHLORICUM

Hydrochloric Acid. HCl

Syn.—Muriatic Acid. Spirit of Salt.

Source.—Obtained by dissolving hydrogen chloride in water. Contains 32 p.c. w/w of HCl.

Characters.—A *colourless*, strongly acid liquid emitting white fumes; sp. gr. 1·158 to 1·168.

Incompatibles.—Lead and silver salts, alkalies and their carbonates.

Official Preparation

1. **Acidum Hydrochloricum Dilutum.**—Contains 10 p.c. w/w of hydrogen chloride. Sp. gr. 1.045 to 1·052. **B.P. Dose.—5 to 60 ms. or 0·3 to 4 mils.**

ACIDUM NITRICUM

Nitric Acid

Source.—Prepared by the interaction of sulphuric acid and sodium nitrate; containing 70 p.c. of HNO_3.

Characters.—A clear, colourless, acid liquid, emitting corrosive fumes; sp. gr. 1.42.

Incompatibles.—Alkalies, alcohol, carbonates, oxides, sulphides, oxidisable substances, iron sulphate and acetate of lead.

Non-official Preparations

1. **Acidum Nitricum Dilutum.**—10 p.c. by weight of hydrogen nitrate. *Dose.*—5 to 20 ms. or 0·3 to 1·2 mils.

2. **Acidum Nitro-hydrochloricum Dilutum.**—1 dr contains about 12·5 p.c. w/w of nitric and 13·5 p.c. w/w of hydrochloric acid. *Dose.*—5 to 20 ms. or 0·3 to 1·2 mils.

Pharmacology and Therapeutics

Externally.—Being a powerful **caustic**, strong nitric acid is employed to destroy **chancres, warts, hæmorrhoids, phagedænic sores** and the poison of venomous snakes and rabid dogs. Owing to the formation of nitro-derivatives of tyrosine it stains the skin yellow. Applied diluted (5 to 10 c.c.

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in a bowl of water) it hardens the skin and prevents excessive sweating. As a bath nitro-hydrochloric acid is useful in **chronic hepatic congestion** *(see page 39)*.

Internally.—Hydrochloric acid being the normal acid of the gastric juice aids transformation of the pepsinogen into pepsin and helps digestion of proteins. In the duodenum, acids reflexly excite the flow of pancreatic juice and govern the production of the hormone secretin. Since the entrance of secretin into the blood stream stimulates the formation of bile, hydrochloric acid also acts as a **cholagogue** *(see* cholagogue). These acids are therefore used in gastric disorders preferably with nux vomica or some bitter. As a **stomachic** they are given freely diluted before meals. In fermentative dyspepsia due to the absence of the antiseptic action of the gastric juice, and in other conditions arising from a deficiency of the acid, they are given after food. Given towards the end of gastric digestion they are useful in **intestinal catarrh** and **chronic diarrhœa.** They are also used to reduce the alkalinity of the urine in phosphatic deposits and to stimulate the hepatic action. Hydrochloric acid has been largely used in the treatment of **pernicious anæmia** in 20 to 30 ms. doses, freely diluted, owing to the deficiency of the normal gastric juice so common in this condition. For the same reason it is used in typhoid fever.

To avoid irritation of the throat and stomach it should be given freely diluted, and taken with a glass tube or quill to prevent its action on the teeth.

ACIDUM PHOSPHORICUM

Phosphoric Acid. H_3PO_4

Source.—Obtained by the oxidation of phosphorus in contact with water. Contains 89 p.c. w/w of H_3PO_4.

Characters.—A colourless, *syrupy* liquid; taste and reaction acid; sp. gr. 1.75.

Incompatibles.—Alkalies, carbonates, ferric chloride, lead salts and calcium salts.

Official Preparation

1. **Acidum Phosphoricum Dilutum.**—10 p.c. w/w of phosphoric acid. **B.P. Dose.—5 to 60 ms. or 0.3 to 4 mils.**

Pharmacology and Therapeutics

Internally.—The diluted acid is a **refrigerant and gastric tonic.** It does not derange the digestion. It makes an agreeable drink in **diabetes** and **febrile diseases.** By some it is considered serviceable in cases of **hypo-phosphaturia.** It has no virtues of free phosphorus.

ACIDUM HYPOPHOSPHOROSUM DILUTUM

Dilute Hypophosphorous Acid

Source.—May be prepared by the interaction of barium hypophosphite and dilute sulphuric acid. Contains 10 p.c. w/w of H_3PO_2.

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Characters.—A clear, colourless liquid; odourless; taste, strongly acid. Miscible with water, and with alcohol (90 p.c.).

B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

Uses.—It has the same action as other acids and being a powerful reducing agent is added to Syrupus Ferri Iodidi as a preservative. It is largely used in the form of hypophosphites, or as Syr. Hypophosph. Co.

ACIDUM SULPHURICUM

Sulphuric Acid

Source.—Obtained by the oxidation and hydration of sulphur dioxide. Contains not less than 95 p.c. w/w of H_2SO_4.

Characters.—A colourless, corrosive, oily, acid liquid, evolving heat when water is added. Sp. gr. 1.84.

Incompatibles.—Alkalies and their carbonates, lead, silver, barium, calcium and strontium salts.

Official Preparation

1. **Acidum Sulphuricum Dilutum.**—10 p.c. Sp. gr. 1·064 to 1·073. The acid must be added to the water. **B.P. Dose.—5 to 60 ms. or 0.3 to 4 mils.**

Non-official Preparation

1. **Acidum Sulphuricum Aromaticum.** *Syn.—Elixir of Vitriol.*—Mix sulphuric acid 70 mils, with alcohol (90 p.c.) 600 mils, add tr. ginger 250 mils, sp. cinnamon 15 mils, add alcohol (90 p.c.) to 1000 mils. *Dose.*—5 to 20 ms. or 0.3 to 1.2 mils.

Pharmacology and Therapeutics

Concentrated sulphuric acid has a strong affinity for water and is a powerful irritant and caustic. Freely diluted it is used as a drink to allay thirst in cholera and as a **mild hæmostatic** to check gastric and intestinal hæmorrhage. It is eliminated by the kidneys and the bowels as a sulphate. Dilute acid or the Elixir of Vitriol is largely used in the treatment of **diarrhœa** and **cholera.**

It prevents absorption of lead by forming an insoluble sulphate, and therefore lemonade made with sulphuric acid is largely used by workers in lead factories as a prophylactic against plumbism.

General Pharmacology of Acetic, Citric, Tartaric, Hydrochloric, Nitric, Phosphoric, Hypophosphorous, and Sulphuric Acids

Externally.—All these acids owe their property to the presence of hydrogen-ion. They **neutralise alkalies,** have a strong affinity for water, and in concentrated solution **coagulate proteins.** Acid solutions check the automatic movement of plain muscles and diminish the height of contraction to electrical stimulation of the striped muscle. These effects on isolated organs are proportional to their power of dissociation, and can be checked by neutralising the acid by an alkali. Acids are therefore **protoplasmic**

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poisons. The hydrogen-ion in organic acids, *e.g.* citric acid, being less dissociable, these are less powerful than the inorganic acids, where the hydrogen-ion is easily dissociated.

In concentrated form they are powerful **irritants** and **caustics,** and by penetrating into the skin and subcutaneous tissues cause severe **pain** and **necrosis,** and if extensive, produce symptoms of **shock** and **collapse.** Hydrochloric acid is less destructive, while concentrated organic acids are still less so, but may cause blisters and are only caustics. Dilute solutions, specially sulphuric acid, are local **astringents** and **styptics.** The organic acids freely diluted act as **refrigerants** and **anhydrotics.**

Internally. **Alimentary canal.**—The corrosive action of the concentrated acids is more marked when applied to a mucous surface. Thus when swallowed they cause severe burning and destruction of the mucous membrane of the mouth, stomach, œsophagus, etc., followed by severe shock, collapse and death. Recovery rarely takes place, but it is always accompained by contraction due to cicatrix formation, difficulty of deglutition and eventually death from inanition.

Diluted acids have a peculiar sour taste and are mild astringents. They soften the enamel of the teeth and reflexly increase salivary secretion and allay thirst. In the stomach they neutralise free alkali and form neutral salts. Since pepsin acts in the presence of free acids, acids, specially hydrochloric acid, play an important part in the process of digestion, and act as an **antiseptic.** The presence of free acid in the stomach is believed to open the pylorus, while its presence in the duodenum causes reflex closure of the pylorus which does not open till the contents have been neutralised by the intestinal juices. Acids also help the formation of secretin which in its turn increases pancreatic secretion.

Blood and tissues.—Acids are rapidly absorbed and circulate as salts formed by neutralising the alkalies of the body. They therefore reduce the alkalinity of the blood, and if the acids are absorbed in large quantities, sufficient to neutralise the fixed alkalies of the body, the alkalinity of the blood is so reduced that the animal dies of acidosis. This however is only possible in herbivorous animals, while in carnivorous animals and in man, the fixed alkalies are spared by the neutralisation of the acids by ammonia (*see* Acidosis).

Kidneys.—Acids are eliminated as neutral or acid salts, and as a result of salt action act as **diuretics.** But the urine is rendered more acid from the formation of acid salts which may cause irritation of the kidney and the genito-urinary mucous membrane. Nitric acid is partly converted

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into ammonia and tends to increase the alkalinity of the blood. The organic acids, viz. acetic, citric and tartaric, are oxidised in the body into carbonates and make the urine alkaline.

Acute toxic action.—All these acids are **irritant poisons.** If swallowed in a concentrated form, intense burning pain extending from the mouth to the stomach, excoriation, and formation of grey or yellowish eschar in the mouth, severe abdominal pain and tenderness, vomiting of coffee-coloured matter containing dark clots of blood and shreds of mucus, constipation, or if bowels are open, stools dark from the admixture of blood are the prominent symptoms. Dyspnœa due to laryngeal swelling, either from irritant fumes or from the introduction of some of the acid, is not infrequent. Collapse with cold perspiration soon sets in and the patient dies.

Antidotes.—*No pump.* Alkalies, such as soda, lime water, soap water, magnesia in a moderately diluted solution at once. Demulcents, as egg albumin, bland oils, linseed tea, etc. Morphine subcutaneously to relieve pain ; ether, brandy, etc., as stimulants.

ACIDUM LACTICUM

Lactic Acid. Hydrogen Lactate. $HC_3H_5O_3$

Source.—Obtained by the lactic fermentation of sugar.

Characters.—A colourless, syrupy liquid ; hygroscopic, inodorous ; sp. gr. 1·21. *Solubility.*—Freely in water, alcohol, (90 p.c.), and ether.

B.P. Dose.—5 to 20 ms. or 0·3 to 1·5 mils.

PHARMACOLOGY AND THERAPEUTICS

Externally.—The concentrated acid is **corrosive** and is used alone or in the form of a paste with kaolin to destroy **lupus.** A lotion (1 p.c.) is used to wash abscess cavities. Because of its low toxicity, it is used as a mild antiseptic and caustic for mucous surfaces, and a 10 p.c. solution is used as a douche in **leucorrhœa** ; while in the form of a jelly or pessary containing 1 to 2 p.c. of the acid with boracic acid it is used as a **contraceptive.**

Internally.—A 10 to 50 p.c. solution in glycerin has been sucessfully applied to **pharyngeal tubercles** after scraping, the strength is slowly increased till pure acid is used. As a pigment or spray it is occasionally used to dissolve **false diphtheritic membranes.** On the stomach it acts like hydrochloric acid and is often given as a **gastric adjuvant** in **dyspepsia.** It allays thirst in **diabetes** and other diseases. Sour butter-milk may be used as a substitute for the same purpose. It is considered to be a valuable intestinal disinfectant, specially of the large bowel. It is useful in the **diarrhœa of phthisis,** of **enteric fever,** and in the **green diarrhœa of infants.** The usual practice is to give 7½ ms. three times a day after food. Infants thrive better on milk to which lactic acid has been added in the proportion of 1 dr. to 1 pint. It enters the blood as a lactate, and is eliminated in the urine as a carbonate or carbonic acid.

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Soured milk at one time was very popular in the treatment of diseases of the **large bowel, colitis, chronic dysentery,** etc., and also in the **summer diarrhœa** of infants. To be free from danger it is absolutely necessary that certain precautions be taken in the preparation of this soured milk. The milk used must first be sterilised to get rid of all contaminating and undesirable organisms. To this sterilised milk some reliable preparation of lactic acid bacilli must be added, *e.g.*, trilactin tablets or liquid trilactin, fermen lactyl, etc.; the vessel containing the milk is then covered and allowed to stand in a warm place, or a thermos flask may be used. After being thus incubated for from six to ten hours the milk is ready for use. From one to three pints may be taken daily. Cream, sugar, etc., may be added to render the preparation more palatable.

GROUP III

HEAVY METALS

The drugs belonging to this group have many properties in common, but individually they have some very important actions and therapeutic uses of their own. For instance, mercury is *antisyphilitic*, iron *hæmatinic*, while others are more or less *astringents* and *caustics*. In the form of pure metals they have practically no action, except a mechanical one, but become active only when used in the form of compounds, and are thus capable of dissociation into ions. Iron and mercury are the only metals that are used in the pure form, all others are used either as organic or inorganic compounds. The more completely dissociated the ions of the salts are, the more rapid and more intense is the action. Thus the inorganic salts are more active than the organic preparations and double salts, which are less readily ionised.

All the salts precipitate proteins and form albuminates of variable composition. In concentrated solutions the precipitate extends into the cells and may have an irritant or even a caustic effect, causing the death of the tissues. They are therefore **astringents, irritants** or **caustics,** according to the strength and preparation used. As a rule the acid ion is more important for the local action than the metal. The chlorides and nitrates are dissociated most rapidly and are **corrosives,** the sulphates are dissociated less rapidly and are less irritant, while the acetates, tartrates and citrates are least corrosives. Of the different salts, lead and alum are astringents, perchloride and nitrate of mercury are irritants, and zinc, copper, silver are irritants or astringents according to the strength of the solution used.

The salts of the heavy metals are very slowly absorbed and slowly excreted, and are therefore more or less cumulative. Chronic poisoning by some of the metals may follow

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the repeated use for a long time even if the dose be very small. Mercury, however, is the only metal that is absorbed freely from the alimentary tract. Except mercury, excretion of these metals *via* the kidneys is less. They are mostly stored up in various organs, chiefly the liver, the spleen, the kidneys and the bone-marrow. In large doses they may produce nephritis. All are more or less astringents, and some, specially lead is constipating, while mercury is a purgative. The nervous system is sensitive to these metals. Disturbances of psychical centres, delirium, mania, peripheral neuritis, and sclerosis of the brain and cord are some manifestations of poisoning from heavy metals.

Many salts of heavy metals are powerful disinfectants, perchloride of mercury is however extensively used as such. Their action is due to the precipitation of the protiens of the microbes, and a specific poisonous action on the bacteria themselves. The action of mercury is however complex; the metal is first adsorbed upon the surface of the bacteria and then enters and kills the bacteria. It therefore takes a longer time to act and will produce its germicidal action even in low concentration provided sufficient time is given. Naegeli has found that some metals in infinitesimal quantities kill algæ, infusoria and bacteria, which has been termed *oligodynamic action* of the drug. In practical therapeutics this oligodynamic action is produced by the colloidal metals. As these are not dissociated into ions they are not irritants, but the free ions present are pharmacologically active: although not powerful enough to produce any local irritation they have a powerful bactericidal effect in very dilute solutions.

Colloidal Metals.—Since the vital processes of the body fluids and living tissues are colloidal phenomena, it has been suggested that if therapeutic agents could be administered in colloidal form they will react with the body tissues where colloidal conditions prevail. A substance is said to be in colloidal state when its particles are sufficiently finely divided in sub-microscopic size as can be kept in solution without mechanical suspension. Colloidal solutions resemble true solutions in so far that the particles remain in suspension and do not form deposit as happens when a mechanical suspension is made. The particles in colloidal solution do not separate out in the liquid owing to Brownian movement and to the electric charges which they carry. In some this charge is positive, but in the majority it is negative, and the mutual repulsion of similarly charged particles keep them in suspension. Colloidal metal is obtained by passing an electric arc between metallic wires under water, when the metal remains evenly and permanently distributed in the solution in very fine subdivision. The metal exists in non-ionisable form and therefore does not cause any irritation, but

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becomes active by slowly passing to the ionic form by the action of bacteria. They have been credited of possessing certain properties in common with ferments.

The use of colloidal solutions in medicine is based on the fact that the minute particles remaining in solution give a larger surface area and therefore confer greater activity. Thus colloidal kaolin, owing to larger surface area, possesses a greater adsorptive power than ordinary kaolin. Colloidal metals have been extensively used as internal antiseptics in many forms of infections, chiefly puerperal and other septicæmias, but with doubtful results. Colloidal lead has been used in the treatment of cancer, and silver in the form of electrargol in septic conditions and infections. They are used hypodermically and even intravenously. The injections are followed by a rise of temperature (sometimes hyperpyrexia) and leucocytosis. Their gradual transformation into the ionic form will elicit the typical action of the metal.

The heavy metals are classified as follows : –

Class A : Antisyphilitic and antiseptic : **Mercury**
Class B : Hæmatinic : **Iron**
Class C : Astringents : **Lead, Silver, Zinc, Copper, Alum**
Class D : Alterative : **Gold**
Class E : Depilatory : **Thallium**

Of these **Mercury** will be discussed with other Chemotherapeutic Agents, and **Iron** with drugs acting on the blood.

Astringent Metals

Lead, Silver, Zinc, Copper, Alum

PLUMBI ACETAS

Lead Acetate. $Pb(C_2H_3O_2)_2,3H_2O$

Syn.—Sugar of Lead.

Source.—Obtained by the interaction of lead oxide and acetic acid. Contains not less than 99·5 p.c. of pure lead acetate.

Characters.—Small, white, monoclinic prisms, or heavy crystalline masses; slightly efflorescent; odour, acetous; taste, sweet, astringent. *Solubility.*—1 in 2·5 of water, 1 in 30 of alcohol (90 p.c.).

Incompatibles.—Mineral and tannic acids and their salts, alkalies, lime water, chlorides, iodides, preparations of opium, mucilage of acacia, albuminous fluids and hard water.

B.P. Dose.—½ to 2 grs. or 0·03 to 0·12 grm.

Official Preparation

1. **Suppositorium Plumbi cum Opio.** *Syn.—Suppositorium Plumbi Co.*—3 grs. of lead acetate and 1 gr. of opium in each.

Non-official Preparation

1. **Pilula Plumbi cum Opio.**—Lead acetate 80, opium 12, syrup of glucose 8 or q.s. 12 p.c. opium. *Dose.*—2 to 4 grs. or 0·12 to 0·25 G.

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LIQUOR PLUMBI SUBACETATIS FORTIS

Strong Solution of Lead Subacetate

Syn.—Goulard's Extract.

Source.—Prepared by dissolving lead acetate in water, adding lead monoxide; filtering and washing the filter.

Characters.—A clear, colourless alkaline liquid, becoming turbid from exposure; taste, sweet, astringent; reaction, alkaline. Sp. gr. 1·28. Contains 19 to 21·5 p.c. of subacetate.

Official Preparation

1. **Liquor Plumbi Subacetatis Dilutus.** *Syn.—Goulard's Lotion; Goulard Water.*—1 in 80 of strong liquor.

Non-official Preparation

1. **Lotio Picis Carbonis et Plumbi, B.P.C.**—Solution of coal tar, 300 ms.; strong solution of lead subacetate, 300 ms.; distilled water, q.s. 20 oz.

PLUMBI MONOXIDUM

Lead Monoxide. PbO

Syn.—Litharge. Plumbi Oxidum. **Syn. I.V.**—*Mudra sung*, Beng.

Source.—Prepared by the oxidation of molten lead.

Characters.—Pale brick-red, or pale orange, heavy scales or powder.

Solubility.—Completely in dilute nitric and acetic acid, insoluble in water.

Enters into.—The preparation of Liq. Plumbi Subacet. Fort.

Official Preparation

1. **Emplastrum Plumbi.** *Syn.—Diachylon or Litharge Plaster; Emp. Plumbi Oleatis, U.S.P.*—A pale yellow solid, being a crude oleate, palmitate, and stearate of lead.

Non-official Preparation

1. **Unguentum Plumbi Oleatis, B.P.C.** *Syn.—Diachylon Ointment; Hebra's Ointment.*—Lead Plaster 50, Ol. Lavender (by weight) 1. Olive Oil (by weight) 49, melt with heat. Useful in *eczema*, excessive perspiration of feet and *sycosis*.

Action and Uses of Lead Monoxide

The oxide has desiccant properties but it is scarcely ever used. Emplastrum plumbi is the basis of most of the plasters. It serves mechanically to hold the lips of *wounds* together, protects irritable surfaces, and by its pressure, helps the absorption of effused products or indolent enlargements.

Pharmacology of Lead Salts

Externally.—Lead salts have a feeble action on the unbroken skin, but on the denuded and exposed mucous membrane, wound and ulcer, they produce precipitation of discharges and form an impervious coating on the surface.

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Since the metal contained in the precipitate has no destructive effect on the cells like mercury, it is not corrosive, on the other hand it has a sedative action and allays itching. It coagulates the albumin of the tissues. Lead therefore is an **astringent, antiphlogistic** and **local sedative.**

Internally.—Insoluble lead salts have no taste, the soluble salts are astringent and sweetish. They have the same local action in the mouth, stomach and intestine as on the skin, and are converted into an albuminate and absorbed as such. The unabsorbed portion is eliminated by the stool as sulphide colouring it leaden black. They cause **constipation** and stop hæmorrhage from the intestine. The action is due to retardation of peristalsis and a diminution of secretion due to astringent action.

Absorption and elimination.—Lead salts enter the blood from the alimentary canal, skin, and the respiratory tract. Lead enters the blood more slowly than any other heavy metal except mercury, and being excreted slowly, it is apt to accumulate in the body. The central nervous sytem, kidneys, liver and the bone are the principal organs where it is deposited. It is excreted slowly by the urine, bile, sweat, milk and the intestine.

The action is best studied from cases of *chronic poisoning.*

The symptoms are characteristic, and involves the nutrition and the condition of the blood. Loss of appetite, nausea, impaired digestion, obstinate constipation, a sweet metallic taste in the mouth, intestinal colic (**lead colic**), formation of a *blue line on the edges of the gums*, are the early symptoms. The blue colouration is due to deposit of lead sulphide, the sulphur being obtained from the food and the tartar of the teeth, and does not occur if the teeth and mouth are kept clean.

Lead colic may sometimes be very severe, and is due to spasm of the intestine. The cause of this is not definitely known, although it has been suggested as being the result of direct action on the plain muscles, like the uterus. The contractions are not co-ordinated as happens in peristaltic movements, but result from spasmodic contractions of the localised circular muscles only. Therefore no purgation follows, on the contrary there is severe constipation. Some however hold that the contraction is due to vascular spasm, and is relieved by amyl nitrite.

Anæmia is common and is sometimes the only symptom. It may be due to malnutrition but mainly to destruction of red blood corpuscles, and the changes in red bone marrow are secondary to anæmia. A very characteristic condition of the blood is the appearance of **basophylic stippling.** There is an increase of leucoblastic cells with disappearance of fat, followed by gelatinous degeneration and atrophy. **Leucocytosis** is common.

The effect on the uterine muscle is responsible for **menorrhagia.** and **abortion** in pregnant women, and for this reason lead plaster is often administered with criminal intent. Peripheral vessels become powerfully constricted resulting in **arterio-sclerosis** and **high blood-pressure.** This at one time was thought to be reflex from pain, but since it is permanent and remains after the subsidence of pain, which is spasmodic, it must be the result of direct action on the arterial muscle. In the same way the heart muscle is also affected although the actual amount of work done is not increased.

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Severe cramps of the leg next appear followed by paralysis of the extensors of the forearm, leading to **wrist drop** from chronic peripheral neuritis of the motor nerves supplying the muscles. The affected muscles become the seat of fatty degeneration, but it is to be noted that the supinator longus escapes. The paralysis may extend to other muscles and there may be general paraplegia and hemiplegia.

Occasionally marked cerebral symptoms are seen leading to **lead encephalopathy**. The onset may be gradual or sudden with vertigo, violent headache, tinnitus, strabismus and other cerebral manifestations like stupor, weakness and tremors. Saturnine lunacy and saturnine epilepsy may result from the action of the poison on the nervous centres. Also optic neuritis and blindness (**lead amblyopia**). This may be the sequence of albuminuric retinitis or effusion into the optic sheath.

As lead prevents excretion of urates from the blood, gouty inflammation of joints often ensues, specially in patients with a gouty diathesis. Chronic lead poisoning is also a common cause of granular kidney with all its attendant symptoms.

Tetra-ethyl of lead is now used with petrol, but gives rise to highly poisonous and toxic fumes. It is freely absorbed by the lungs and skin. The symptoms are the same as lead.

Treatment.—Conditions favouring calcium retention help storage of lead in the bones, and therefore calcium lactate, or milk (because of its high calcium content) should be given during the acute symptoms to help deposition of lead in the bone. After the acute symptoms are over efforts should be made to help excretion by low intake of calcium, and by acids like phosphoric acid, or ammonium chloride. Atropine and belladonna relieve colic and constipation. Potassium iodide to dissolve insoluble compounds of lead and magnesium sulphate to remove them from the system, and prevent their reabsorption after they have been eliminated into the intestine. Morphine for colic, sulphur baths to help elimination by the skin.

Acute toxic action.—Concentrated solutions of lead salts are irritant. Acute poisoning is rare, but has recently not been infrequently seen on account of the use of diachylon plaster as an abortifacient. Abortion certainly follows its administration, but acute plumbism leading to paralysis, blindness, insanity, and death also sometimes occur. Burning pain in the stomach, dryness of the throat, thirst, vomiting, colic, constipation with slate coloured stools, cold sweats, cramps in the legs, collapse; sometimes even stupor, coma, and convulsions are some of the symptoms induced by the acetate.

Antidotes.—Stomach-pump, zinc sulphate both as an emetic and antidote, followed by milk or the white of egg; dilute sulphuric acid. Calcium to help storage in the bones. Sodium and magnesium sulphate produce insoluble sulphates and open the bowels. Morphine or demulcent drinks to relieve colicky pain.

Therapeutics of Lead Salts

Externally.—Generally speaking, lead salts are useful in a variety of diseases:—(1) To *soothe irritation and control excessive discharge,* the lotions and ointments are employed in inflamed, painful, weeping **eczema,** irritable **ulcers** and **wounds.** The lotion may be used in **vulvitis, leucorrhœa, otorrhœa,** etc. A lead and opium lotion (Tr. opii 10 ms., liq. plumb. subacet. dil. 1 dr. and water to 1 oz.) is a good sedative application to **bruises, sprains** and other **cutaneous inflammations.** Diachylon ointment, alone or combined with zinc oleate or mercuric oleate ointments, makes a very effective non-irritant application. (2) To *allay irritation and*

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itching, a lotion or ointment is used in **pruritus pudendi** (the cause being first removed), **urticaria**, etc.

Internally.—For its local astringent effects, Glycerinum Plumbi Subacetatis (strong solution of lead subacetate 5, glycerin 5, water q.s.), or a gargle can be used in **tonsillitis, pharyngitis**, etc. Lead acetate is the only salt that is used internally. Its chief use is to check severe **diarrhœa** and **hæmorrhage** from stomach and bowels as in **typhoid fever** and **tuberculosis**. Pilula plumbi c. opio is a valuable preparation in such cases. Lead suppository or an enema of acetate of lead may be employed to arrest **rectal hæmorrhages**, and as an **astringent** in **chronic dysentery**.

Recently the use of colloidal lead in the treatment of **cancer** has been suggested by Blair Bell, but the treatment is still in its experimental stage and is attended with great risk of poisoning. Moreover, great care is required in the preparation of the compound and regulation of the dosage.

ARGENTI NITRAS

Silver Nitrate. $AgNO_3$

Syn.—Lunar Caustic.

Source.—Prepared by the action of nitric acid and silver.

Characters.—Colourless, tabular crystals. Taste, bitter, metallic.

Solubility.—2 in 1 of water.

Incompatibles.—Alkalies and their carbonates, bromides, chlorides, phosphates, iodides, acids (except nitric and acetic), alkaloids, and solutions of arsenic and tannin.

B.P. Dose.—$\frac{1}{8}$ to $\frac{1}{4}$ gr. or 0.008 to 0.016 grm.

Official Preparation

1. **Argenti Nitras Induratus.** *Syn.—Toughened Caustic.*—Greyish-white, or white cylindrical rods or cones. Freely soluble in distilled water and sparingly soluble in alcohol (90 p.c.). Obtained by fusing silver nitrate 95 parts and potassium nitrate 5 parts and pouring into moulds.

Non-official Preparations

1. **Choleval.**—Colloidal silver with sodium cholate. *Antiseptic* and *hæmostatic.* Useful in gynæcological practice. For vaginal irrigation 0.5 grm. in half a litre of water. Does not coagulate albumin. Powerful bactericide, specially for gonococci. Antiseptic and astringent for uterine irrigation.

2. **Argentum Colloidale** (Crede's). *Syn.—Collargolum.*—Metallic silver in a colloid state. Its ointment (Argen. Coll. 15, Cera Alba 10, Adep. Benz. 75) is used as a prophylactic to *gonorrhœal ophthalmia.* *Dose.*—$\frac{1}{2}$ to 2 grs. or 0·03 to 0·12 grm. in pills or solution.

3. **Argento-proteinum Forte, U.S.P.** *Syn.—Protargol.*—A compound of silver and protein, containing 7.5 to 8.5 p.c. of silver. A powerful germicide. A $\frac{1}{2}$ to 1 p.c. solution makes a painless injection in *gonorrhœa.* A 2 p.c. solution as a prophylactic against *gonorrhœal infection*, and internally in continued acute *catarrhal diarrhœa.* $\frac{1}{2}$ to 1 p.c. or up to 10 p.c. useful in *ophthalmia.* Urethral irrigation—1 in 2000 to 1 in 1000; bowel wash, 0.1 p.c.

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4. **Argento-proteinum Mite, U.S.P.** *Syn.—Argyrol; Mild Protargin.*—Silver rendered colloidal by the presence of or combination with protein. Contains 19 to 25 p.c. of silver. Dark brown or almost black shining scales or granules. Very soluble in water, but not in alcohol. An excellent non-irritating application for mucous membranes. In *colitis* 1 p.c. solution as enema. For *cystitis* use 1 in 5000 solution. As a mild caustic 1 in 100. In ophthalmic practice as a *prophylactic* against ophthalmia neonatorum 25 p.c. In *gonorrhœa* as a prophylactic, 10 p.c.; urethral irrigation, 1 in 1000. Bowel wash, 0.1 to 1 p.c.

5 **Albargin.** *Syn.—Silver Gelatose.*—Contains 15 p.c. of silver. A 0.2 p.c. solution useful as an injection in *gonorrhœa*. A 0.25 p.c. solution as a bowel wash in dysentery.

Pharmacology of Silver Salts

Externally.—Soluble silver salts unite chemically with the proteins of the tissues and discharges to form albuminates, but their action does not penetrate into the deeper tissues and is checked by sodium chloride which changes it into inert silver chloride. Applied to the unbroken skin in the form of a stick or in concentrated solution, it produces at first a white stain which soon turns black from exposure to light. The stain peels off as a dark scale if the application is light, or as a black slough if the application is prolonged. It is therefore an **astringent** and **caustic**.

It is an **antiseptic** but as soon as it comes in contact with any secretion of the body or with any tissue it is precipitated as inert silver chloride. The antiseptic action is due to its forming compound with proteins of the bacteria, but since it also combines with the proteins of the tissues there is irritation which is more marked when applied to delicate mucous membrane like the conjunctiva. The protein compounds being non-ionisable are not precipitated and therefore are less irritant and feebly disinfectant. For the same reason the colloidal compounds are not corrosives nor irritants or astringents. They have no antiseptic action even after prolonged application, the antiseptic action depending upon the ionic concentration of the different compounds.

Internally.—In the mouth and stomach silver acts as an **astringent**. It has no astringent effect in the intestine as it is precipitated as silver chloride in the stomach and reduced to metallic silver in the intestine. Moderately large doses cause gastro-enteritis with collapse and death. Silver is not absorbed in sufficient quantity to produce any general effect, but if the administration is prolonged it is absorbed in very minute quantities, and the granules are deposited in the various parts of the body, chiefly the mouth and the gums, producing dark blue discoloration resembling lead poisoning. It causes a slate **blue discoloration** of the skin from deposition of the compound in all tissues of the skin except the rete Malpighii. This pigmentation or

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argyria is almost permanent. The same discoloration is also noticed in the conjunctiva from prolonged application of silver compounds and deposition of silver albuminate in the sub-epithelial tissue. The colouring sometimes spreads to the cornea when the vision is interfered with. This condition is known as **argyrosis** of the conjunctiva, and may be removed by the injection, after preliminary anæsthesia, of a solution of 12 p.c. sodium thiosulphate and 2 parts of a 2 p.c. solution of potassium ferrocyanide, with a fine platinum needle subconjunctivally.

Elimination.—Silver is excreted with the fæces as sulphide staining it dark brown, and by the intestinal secretion and bile. A portion is deposited in the kidneys and the liver.

Toxic action.—When given in poisonous doses the only symptoms produced are those of gastro-enteritis with vomiting and purging, extreme prostration, collapse and death. When given to animals the chief symptoms are those of central nervous system. They are paralysis of the vaso-motor centre with fall of blood-pressure, disturbances of respiration and finally paralysis of the respiratory centre, general convulsion followed by paralysis beginning in the lower extremities. The heart is little affected, in fact it continues to beat even after the stoppage of respiration.

Antidotes.—In *acute poisoning* from accidental causes, mucilaginous drinks, such as thick gruel, should be immediately given to envelope the caustic ; this should be followed by an emetic or stomach syphon. Common salt is the *chemical antidote.* White of egg, milk and water, and other demulcents may be given freely.

Therapeutics of Silver Salts

Externally.—Silver nitrate may be applied to **exuberant granulations, callous, indolent ulcers, fistulæ, chancres,** etc., because of its limited caustic and after-stimulating effects on them. It is a valuable caustic for **post-mortem wounds,** but not a reliable one for bites by poisonous snakes and rabid animals, as its action does not penetrate into the deeper layers. It arrests **bleeding** from **leech-bites.**

Eye and nose.—A solution of siver nitrate (5 to 10 grs. in 1 oz.) is useful in **granular conjunctivitis** and **ophthalmia neonatorum.** As a preventive against ophthalmia neonatorum, both nitrate (1 to 2 p.c.) and protargol are largely used, the latter up to 10 p.c. solution. The conjunctiva must first be rendered anæsthetic by means of cocaine. The silver solution is then applied with a camel-hair brush, and the excess of caustic afterwards neutralised by irrigation with normal saline solution. A weaker solution (1 to 4 grs. in 1 oz.) may be used as a collyrium in **purulent conjunctivitis.** A weak solution makes a valuable irrigation in **rhinitis.** Both protargol and argyrol may be used in conjunctivitis as

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eye-drops; the former in strengths of 2 to 20 p.c., while the latter 25 p.c. A 10 p.c. ointment of argyrol may also be used.

Genitals.—Solid caustic is still used for cauterising **granular** or **ulcerated os** and **cervix.** A strong solution may be injected into or painted within the womb in **endometritis** or **endocervicitis.** A weaker solution (1 to 2 grs. in 1 oz.) makes an effective injection in **gonorrhœa, leucorrhœa** and **pruritus pudendi** due to leucorrhœa. Irrigation (1 in 1000 to 10,000) has been successfully used in many cases of gonorrhœa. Injections of protargol or argyrol are also useful. Being opaque to X-rays, collargol (20 p.c. solution) is injected into the ureter and renal pelvis for diagnostic purposes.

Internally. **Alimentary canal.**—Unhealthy or chronic **ulcers** in the mouth quickly heal after being touched with mitigated caustic. A solution (10 to 20 grs. in 1 oz.) is an excellent application for **sore throat,** acute or chronic, **pharyngitis, follicular tonsillitis,** and **tubercular** and other **ulcerations** of the **larynx.**

It has been used in chronic diarrhœa, vomiting and in gastric ulcer without much benefit. As an enema (10 grs. to 1 pt.), it has been successfully employed in **chronic dysentery** and **ulcerations** of the **bowel.** Albargin 1 to 2 grains to 1 oz. makes an excellent bowel wash in cases of chronic bacillary dysentery and in colitic conditions. It should be used after a preliminary washing of the bowel with plain warm water.

Nervous system.—Silver was formerly much esteemed in many nervous diseases, specially **epilepsy,** but it is doubtful if any silver actually reaches the central nervous system, and the clinical experience has been disappointing. Moreover the unpleasant symptoms of argyria are the chief barrier to its use, and on this account nitrate of silver is now very rarely used by neurologists.

Caution.—To avoid argyria, the use of the drug must be suspended as soon as a dark line is noticed on the edges of the gums which may be removed by a course of acid tartrate of potassium, or potassium iodide. But perfect restoration to the normal does not occur. Its administration must be stopped for two weeks after two months' use, however small the dose may be. The use of hexamine has given good results in some cases.

Silver stains on linen can be removed by washing with a solution of potassium cyanide 3 gms., iodine 0.3 gm., and water 30 c.c. The stain on the skin may be removed (1) by potassium cyanide solution, but the part must be well washed afterwards. (2) by covering the skin with solution of iodine and then washing with a solution of sodium thiosulphate, or (3) by washing with corrosive sublimate solution.

Prescribing hints.—Silver salts are given in pills after food, but if their local action on the stomach is desired they should be given on an empty stomach, preferably in solution.

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For application to the skin, a solution of the nitrate in nitrous ether is the best, as it does not run in drops and is a stronger preparation than the aqueous solution. The ordinary silver preparations have been largely replaced by argyrol, protargol and colloidal preparations.

ZINCI CHLORIDUM

Zinc Chloride. $ZnCl_2$

Source.—Obtained by the interaction of zinc and hydrochloric acid.
Characters.—Colourless, opaque, deliquescent rods or masses, or in granular powder; powerfully caustic. *Solubility.*—Freely in alcohol, and glycerin.

Pharmacology and Therapeutics of Zinc Chloride

The chloride is a powerful **caustic** characterised by its property of **burning deeply** and not spreading sideways like caustic potash. It is also painless. Therefore it has been used to destroy exposed tooth pulp in **carious teeth, wart, condyloma** and **lupus.** In dilute solutions (1 in 10 of water) it forms a good stimulating application for ulcers failing to heal from want of vitality. It may also be used as a disinfectant for washing out cavities and wounds with putrid discharge. A weak solution (1 to 2 grs. to 1 pint) forms a useful injection for **gonorrhœa.**

It is the principal ingredient of **Burnett's Disinfecting Fluid,** a well known household disinfectant for cleaning utensils in the sick room of fever patients; it quickly permeates or disintegrates all organic matter with which it comes in contact. The chief objection to its use is that it is highly poisonous, and being devoid of any smell or colour it may be taken accidentally. The chloride is highly corrosive and poisonous and should never be given internally.

ZINCI SULPHAS

Zinc Sulphate. $ZnSO_4,7H_2O$

Syn.—White Vitriol.
Source.—By the interaction of zinc and sulphuric acid.
Characters.—Colourless, transparent crystals, with a strong metallic styptic taste.
Incompatibles.—Alkalies and their carbonates, lime-water, lead acetate, silver nitrate, vegetable infusions, and milk.
B.P. Dose.—1 to 3 grs. or 0·06 to 0·2 grm.; 10 to 30 grs. or 0·6 to 2 grm. as emetic.

Official Preparation

1. **Unguentum Zinci Oleatis.**—Zinc Sulph. 30 p.c.

ZINCI STEARAS

Zinc Stearate

Source.—Prepared by the interaction of a soluble zinc salt and a solution of sodium salt of stearic acid of commerce. Consists

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chiefly of zinc stearate and variable proportions of zinc palmitate. Contains not less than 13 p.c. and not more than 15.5 p.c. of zinc oxide.

Characters.—A light, white, impalpable amorphous powder, free from grittiness; odour, characteristic. *Insoluble* in water, in alcohol (90 p.c.), and in ether.

Non-official Preparations

1. **Zinci Carbonas.**—A white, tasteless, inodorous powder. Insoluble in water.
2. **Calamina Præparata.** *Syn.—Prepared Calamine.*—Prepared by calcining native carbonate of zinc and reducing it to an impalpable powder and suitably coloured with iron oxide. A pale, pinkish powder, without grittiness.
3. **Lotio Calaminæ.**—Prepared calamine 3 oz., zinc oxide 1 oz., glycerin 1 oz., rose water to 20 oz. In *eczema*, and *to conceal acne spots on the face.*

ZINCI OXIDUM

Zinc Oxide. ZnO

Syn.—Chinese White.

Source.—Obtained from metallic zinc by combustion in air.

Characters.—A soft, white or nearly white, tasteless and amorphous powder, becoming pale-yellow when heated. Insoluble in water.

B.P. Dose.—5 to 10 grs. or 0·3 to 0·6 grm.

Official Preparations

1. **Unguentum Zinci Oxidi.** *Syn.—Zinc Ointment.*—15 p.c.
2. **Pasta Zinci Oxidi Composita.** *Syn.—Zinc Paste; Lassar's paste.*—Zinc oxide 25 p.c.
3. **Gelatinum Zinci.** *Syn.—Unna's Paste.*—Zinc oxide 15 p.c.

Non-official Preparation

1. **Zinci Phenolsulphonas.** *Syn.—Zinc Sulphocarbolate.*—Colourless, transparent, efflorescent crystals. Soluble 1 in 2 of water. As an injection in *gonorrhœa* (2 to 3 grs. to 1 oz.).

Pharmacology of Sulphate, Oxide and Stearate of Zinc

Externally.—The insoluble salts like the oxide, the carbonate and the stearate are mild **antiseptics** and **astringents**, and are used as local sedatives. Their action resembles lead and silver salts, *i.e.*, they precipitate the proteins in the discharges and in the tissues.

Internally.—The sulphate has a metallic taste and acts as an emetic like copper but less irritating, though quite effective and prompt, and not followed by any depression. In large doses it is a powerful **gastro-intestinal irritant** causing vomiting, purging, abdominal pain and collapse. The oxide and the carbonate are less irritant to the stomach, but their prolonged use causes dyspepsia and constipation, and occasionally diarrhœa.

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Zinc is eliminated by the stool, and in smaller amount by the bile and the urine. It is absorbed and stored up in the liver and to a less extent in the spleen, the kidneys, and the thyroid.

Little is known of its systemic effect. After prolonged use the symptoms closely resemble plumbism. In zinc mines of Silesia the workers suffer from obstinate catarrh of the respiratory tract, catarrh of the throat and constriction of the chest, a metallic taste in the mouth, gastro-intestinal irritation, general cachexia, cramps, lassitude and joint pains. Intermittent attacks of fever, known as *brass founder's ague* sometimes occur from constant inhalation of the fumes. Some obscure nervous symptoms have been attributed to it. It depresses the central nervous system, the heart, and the muscles.

THERAPEUTICS OF SULPHATE, OXIDE AND STEARATE OF ZINC

Externally.—The sulphate (2 grs. to 1 oz. of water) forms an excellent and stimulating application for wounds and ulcers, and as an **astringent injection** in **gonorrhœa, leucorrhœa, otitis,** etc. It is used as an eye lotion in conjunctivitis provided there is no ulceration of the cornea.

As a mild astringent and sedative the oxide is used as a dusting powder mixed with talc powder, or as an ointment or paste in various skin affections of children. As it lessens secretion it is used as a drying application in **eczema** and **intertrigo.**

Internally.—The sulphate is used internally as an emetic in cases of poisoning. The oxide has been used in **hysteria** and **epilepsy,** and with belladonna to check the **night sweats of phthisis**; possibly it is of little value in these cases.

CUPRI SULPHAS

Copper Sulphate. $CuSO_4,5H_2O$

Syn.—Blue Vitriol: Blue Stone. **Syn. I.V.**—*Tutia.* Beng., Hind.
Source.—obtained by the action of sulphuric acid on copper.
Characters.—In blue triclinic prisms, or a blue crystalline powder.
Solubility.—1 in 3 of cold water.
Incompatibles.—Alkalies and their carbonates, lime water, mineral salts (except sulphates), iodides, and many vegetable astringents.
B.P. Dose.—$\frac{1}{4}$ to 2 grs. or 0·016 to 0·12 grm.; 5 to 10 grs. or 0·3 to 0·6 grm. as an emetic.

NON-OFFICIAL PREPARATIONS

1. **Lapis Divinus.** *Syn.*—*Cuprum Aluminatum.*—Powdered copper sulphate, potassium nitrate and alum, of each equal parts fused in an earthen crucible. 2 grs. in 1 oz. of distilled water makes a good *eye-wash.*

2. **Unguentum Cupri Oleatis, B.P.C.**—Copper oleate 12·5, yellow soft paraffin 87·5; melt and mix. An excellent antiseptic and parasiticide. Useful in *ringworm,* hard and horny *warts* and *corns.*

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Pharmacology

Externally.—Copper sulphate has no action on the unbroken skin, but is a **caustic** when applied to a raw surface or a delicate mucous membrane, such as that of the conjunctiva. In dilute solutions it constricts local blood-vessels, and it is therefore a **local astringent**. It is an **antiseptic** and in dilutions of 1 in 1,000,000 of distilled water, 1 in 50,000 of tap water, and 1 in 1,000 of sea water kills *B. typhosus* in two hours. The presence of organic matter still further reduces this action. It is highly poisonous to algæ, fungi and protozoa. It is however not a reliable bactericide, though fairly efficacious for the bacilli of the colon group.

Internally. **Gastro-intestinal tract.**—In small doses copper has a harsh metallic taste, and acts as an **astringent**, and in large doses (5 to 10 grs.), as an **emetic** like zinc sulphate. Emesis is caused by its action on the stomach, when it is expelled out and no further action is observed. If it fails to induce vomiting the stomach must be quickly emptied, otherwise gastro-enteritis may result with symptoms of acute corrosive poisoning, causing abdominal pain, vomiting, tenesmus and violent diarrhœa. As a rule large single doses do not cause any harm as they are rapidly removed by vomiting.

Absorption and elimination.—Copper is absorbed with difficulty in minute quantities, either when given by the mouth or from wounds and other mucous surfaces, and is stored up in the liver, spleen and kidneys. It is eliminated almost entirely by the fæces, also by the bile, urine, saliva and sweat.

Copper in minute quantities is present in the mammalian tissue, and is supposed to aid iron in the formation of hæmoglobin in young animals (Hart and Steenbock). It has been shown that a combination of copper and iron improves induced anæmia more quickly than when iron is administered alone. It does not help absorption or storage of iron and does not enter into the formation of hæmoglobin, but is said to act as a catalytic agent in its formation. It is normally present in the food, specially vegetable food, and enters into a firm compound with chlorophyll.

Acute toxic action.—This is rare. In large doses copper salts produce violent gastro-intestinal irritation, causing vomiting sometimes of bluish colour, metallic taste in the mouth, abdominal pain and symptoms of gastro-enteritis. Death may occur from cardiac and respiratory failure.

Antidotes.—Emetics or stomach pump if there is no free vomiting; white of egg, milk or demulcent drinks, yellow prussiate of potassium, followed by opium and a warm poultice over the stomach.

Chronic toxic action.—Workers in copper or brass may suffer from anæmia, headache, debility, emaciation, indigestion, tremors, laryngeal and pharyngeal catarrh, occasional hæmoptysis, salivation, a green line at the bases of the teeth and occasional colic, in short a condition not unlike that of lead poisoning.

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Therapeutics

Externally.—Copper sulphate in the form of sticks is used to destroy **exhuberant granulations,** and as a lotion (2 to 4 grs. to 1 oz.) to stimulate **indolent ulcers.** Being not so strong as silver nitrate, it causes less pain when applied to **granular lids** and to the edges of the eyelids in **tinea tarsi.** It is largely used in the form of *lapis divinus.* Ung. cupræ oleatis is an excellent remedy for **ringworm.** In strengths of 1 in 2 to 10 millions it removes algæ and other vegetable growths from the water.

It has also been used to sterilise water infected with typhoid bacillus, but the proportion of copper is greater than required to kill algæ.

Internally.—Very rarely used internally, but has been recommended in ¼ to 1 gr. doses in **actinomycosis and sporotrichosis.** For its emetic action, it is occasionally used in narcotic poisoning in 1 p.c. solution. It is a valuable antidote in poisoning by phosphorus ; here it acts not only as an emetic, but it forms insoluble copper phosphide which is not absorbed. 3 grs. of copper sulphate should be given every few minutes until vomiting is induced and then a saline laxative.

ALUMEN

Alum

Syn.—Alumen Purificatum.

Syn. I.V.—*Fatkiri,* Beng, *Fitkiri,* Hind.

Sources.—Obtained by the combination of aluminium sulphate with potassium sulphate, and contains not less than 99.5 p. c. of potash alum ; or by the combination of aluminium sulphate with ammonium sulphate, and contains not less than 99.5 p.c. of ammonia alum.

Characters.—Colourless, transparent, crystalline masses, or a white powder ; taste, sweetish and astringent. Melts when heated and loses water of crystallisation and forms anhydrous salt. Very *soluble* in water ; insoluble in alcohol (90 p.c.) ; freely soluble in glycerin.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Official Preparation

1. **Glycerinum Aluminis.—**13 p.c. potash alum **B.P. Dose.—30 to 60 ms. or 3 to 4 mils.**

Non-official Preparations and Allied Derivatives

1. **Collyrium Aluminis, B.P.C.** –Alum, 10 ; distilled water to 1000.
2. **Gargarisma Aluminis, B.P.C.** *Syn.—Alum Gargle.*—Glycerin of alum, 125 mils ; acid infusion of roses q.s. 1000 mils.
3. **Alumini Aceto-Tartras.** *Syn.—Alsol.*—In shining masses, soluble in water. Astringent and antiseptic. 1 or 2 p.c. solution as gargle, lotion or douche.
4. **Aluminii Hydroxidum.**—Prepared by precipitating a boiling solution of alum with sodium carbonate. White, bulky, amorphous powder. Odourless and tasteless. Insoluble in water. *Dose.*—5 to 10 grs. or 0·3 to 0·6 grms. Colloidal aluminium hydroxide tablets are sold under the name of **Alocol.** Useful in *flatulence, hyperacidity, pyrosis,* etc.

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Pharmacology

Externally.—Alum has no action on the unbroken skin, but coagulates the albumin of discharges and tissues. It therefore forms a covering on ulcers and sores, and arrests bleeding. Hence, it is a valuable **local astringent** and **hæmostatic**. Dried alum is a mild **caustic** because it abstracts water.

Internally.—Alum is a local **astringent** to the mouth and throat, imparting an astringent taste, and a feeling of dryness to the throat. In small doses (3 to 4 grs.) it has the same astringent action on the stomach and intestine as on the raw skin, producing **constipation**. Its **hæmostatic** action is entirely local. In 30 to 60 grs. it causes **vomiting** by directly stimulating the peripheral nerves of the stomach, and in still larger doses it is a **gastro-intestinal irritant** causing vomiting and purging. When injected per rectum, it kills **thread worms**.

Elimination.—Alum is probably absorbed into the blood as an albuminate, and has no remote action on the tissues in medicinal doses. It is chiefly eliminated with the fæces and partly by the skin, bile and kidneys.

Therapeutics

Externally. **Skin.**—Being cheap and easily available, alum is used in various minor complaints. In powder or in a concentrated solution, it stops bleeding from **leech bites, wounds**, and **superficial cuts**. A weak solution of alum and borax (1 p.c. of each) checks the discharge of **weeping eczema**.

Nose.—Its solution makes a useful **collunarium** in **ozæna**. Powdered alum either sniffed up or blown in by means of a paper funnel, or its lotion (10 grs. in 1 oz.) injected into the nostrils, arrests **epistaxis**.

Eyes.—Alum makes a useful **collyrium** (4 to 8 grs. in 1 oz.) for ordinary or purulent **conjunctivitis**.

Genitals.—It makes a capital wash (1 dr. in 1 pint) for **vulvitis of children**, if the parts are frequently irrigated and a piece of lint soaked in the lotion is left *in situ*. It also relieves **pruritus**. A douche (10 grs. to 1 oz.) removes **leucorrhœa**, checks slight hæmorrhage from patulous os after abortion or delivery. A weak solution (3 grs. in 1 oz.) is successfully employed in **gonorrhœa** as an injection.

Internally. **Mouth.**—Alum is commonly used as a dentifrice in **ulcerated and spongy gums**. A solution (5 to 10 grs. in 1 oz.) is a useful gargle in **sore throat, elongated uvula, tonsillitis, salivation**, and **aphthous** and **ulcerative stomatitis**, but Glycerinum Aluminis is a better application in these cases. In the form of a spray, alum may be employed in **hoarseness** and **chronic coughs**.

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Stomach and intestine.—As an astringent, alum is used in **chronic diarrhœa** and as a local hæmostatic in **gastro-intestinal hæmorrhage.** Alum-whey obtained by curdling 1 pint of milk with 2 drs. of alum may be given with benefit in **enteric** and other **diarrhœas.** In 30 gr. doses frequently repeated, it is of special value in **lead poisoning** and relieves **colic** by precipitating lead salts as insoluble lead sulphates.

KAOLINUM

Kaolin

Source.—A native aluminium silicate, powdered and freed from gritty particles by elutriation.

Characters.—A soft whitish powder, insoluble in water or in mineral acid.

B.P. Dose.—½ to 2 oz. or 15 to 60 grm.

Official Preparation

1. **Cataplasma Kaolini.** *Syn.*—*Kaolin Poultice.*—Should be kept in well closed containers.

Non-official Preparations

1. **Unguentum Kaolini, B.P.C.** *Syn.*—*Kaolin Mass.*—White soft paraffin 50, hard paraffin 25, melt, and add kaolin 25; stir till cold. An emollient application to abraded surfaces, and a useful excipient for silver nitrate, potassium permanganate, and bichromate pills.

2. **Emulsio Paraffini Liquidi et Kaolini, B.P.C.**—Liquid paraffin, 5 oz.; powdered acacia, 300 grs.; tragacanth powder, 37½ grs.; kaolin 3¾ oz.; chloroform water q.s. 20 oz. *Dose.*—15 to 60 mils or ½ to 2 oz.

Uses

Besides its use as an **excipient** in the preparation of pill masses, specially for substances which are readily oxidised, kaolin can be employed as a dusting powder in **intertrigo, weeping eczema,** etc. The cataplasma forms a valuable poultice in relieving deep-seated inflammation and may be applied hot on a piece of thick cloth or lint in pleurisy, pneumonia, pericarditis, inflamed joints, hepatitis, etc., where it gives much relief. It should be changed every twelve to twenty four hours, and kept in place with a bandage.

Internally.—Kaolin has two important actions, *viz.*, (1) forms a coating on the intestinal wall thus protecting it from irritating particles and digestive juices and which reflexly reduces peristalsis; (2) adsorbs poisons and bacterial toxins. For its former effect it is used in **diarrhœa** and **ulcerative colitis,** while for the latter in **cholera, dysentery,** etc. The usual practice is to mix 100 grm. in 250 c.c. of water, half a pint of this is given every half hour for the first twelve hours, and several glasses are taken during the next twelve hours. Being a very efficient adsorbent **colloidal kaolin** (Osmo Kaolin) is extensively used for

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adsorption of bacteria and toxins from the intestine thus preventing their absorption. *Kaolin has no direct disinfecting action on the intestine.*

ALTERATIVE

Gold

AURI ET SODII CHLORIDUM

(Not official)

Source and Characters.—A mixture of equal parts of anhydrous gold chloride and anhydrous sodium chloride. Orange-yellow powder. Odourless. Taste saline, metallic. Very soluble in water. Yields 50 p.c. gold.

Dose.—1/30 to 1/12 gr. or 0.002 to 0.005 grm.

NON-OFFICIAL PREPARATION

1. **Liquor Auri et Arsenii Brominatus, B. P. C.**—Arsenious anhydride 0.46, potassium carbonate 0.46, bromine by wt. 1.14, gold in leaf (pure) 0.15, water to 100. Contains 1/21 gr. arsenious anhydride and 1/32 gr. gold tribromide in 10 ms.

Dose.—5 to 10 ms. or 0·3 to 0·6 mil.

AURI ET SODII THIOSULPHAS

(Not official)

Syn—Sanocrysin; Crisalbin.

Characters.—A double thiosulphate of gold and sodium. Solid snow-white substance in long needle-like crystals, freely soluble in water, 2 grm. being dissolved by 2 c.c. water. Solution neutral.

Dose.—0.025 gradually increased to 1 grm. in 10 c.c. of distilled water at intervals of 3 to 4 days, intravenously.

SODIUM AUROTHIOMALATE

(Not official)

Syn.—Myocrisin.

A preparation containing 50 p.c. gold.

Dose.—0.01 gm. initial dose, increased gradually to 0.05, 0.1 and 0.2 gm. in 8 to 10 injections.

N.B.—An interval of 4 to 6 weeks should be allowed after one course.

ACTION AND USES

Gold in different forms has been used empirically in diverse conditions. It is much less poisonous than other heavy metals, although its salts when given in toxic doses produce vomiting and purging. Given intravenously it acts like arsenic, and produces a fall of blood pressure by dilating the mesenteric vessels. It is said to help absorption of pathological connective tissues. In combination with arsenic it has been used in **tertiary syphilis**, and with bromides in **epilepsy**. It is used in **neurasthenia**, but any benefit that may follow its use is possibly mental.

The chief interest of gold at the present time centres on its supposed value in **tuberculosis** and Moellgaard introduced it in the form of **sanocrysin**. How it acts is not clearly understood and it has been suggested that it penetrates the lipoid covering of the bacilli which it kills. It is also possible that it stimulates phagocytosis of the reticulo-endothelial tissues. It has no marked effect on tubercle

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bacilli *in vitro*, and Moellgaard claimed that it has a direct bactericidal effect in the animal body. The injections are often followed by some reaction, such as albuminuria, fever, exanthemata, loss of weight and intestinal disturbances. There may also be some focal reaction. These symptoms are likely to occur when an injection is given while the patient still shows a febrile reaction from the previous injection or when the patient is febrile before the first injection is given. They are probably due to an overdosage. Knud Secher believes that the reactions are due to liberation of toxins. He therefore bases his initial dosage on the assumption that in "open cases" the toxins can be excreted by the air passages and therefore larger doses are permissible, while in "closed cases" smaller doses are indicated because the toxins having no outlet pass into the blood stream. An intravenous injection of antitoxic serum prevents the appearance of these symptoms and makes the treatment with sanocrysin more safe. This serum is prepared by injecting calves with tubercle bacillus killed by heat, and with tuberculin. The serum of horses injected with diaplyte (defatted) tubercle vaccine gives better results.

Although it is too early to properly assess its value as a remedy for pulmonary tuberculosis, the reports of the Medical Research Council are favourable. Under its use the tubercle bacillus disappears in early cases and there is diminution of sputum, cough and pyrexia. The 1st report records 2 deaths directly caused by sanocrysin out of 30 cases. Early cases certainly improve but the results are not so favourable in advanced cases. The regulation of the dose is an important factor and if not carefully watched will make the condition worse.

Like other heavy metals sanocrysin produces cumulative effects when given in large doses, or at frequent intervals.

In the form of myocrisin gold is extensively used in the Continent in **rheumatoid arthritis**. It is given itramuscularly, commencing with doses of 0.01 grm. and then slowly working up to 0.2 grm. in 8 to 10 injections, and a total of 2 grm. forms a course. An interval of 4 to 6 weeks is given before starting another course. Generally two to three courses are required. Symptoms of poisoning however follow the treatment, and they are vomiting, albuminuria, neuritis and various skin rashes. Sodium thiosulphate relieves these symptoms.

Combined ionisation and gold treatment has given very favourable results in **lupus**, and its action has been explained as an indirect one, of the nature of a regressive influence on the pathological tissue and upon the altered blood vessels. In **lupus erythematosus**, sanocrysin has been used with good results. The initial dose is 0·001 grm. gradually increased to 0·05 grm. It is given once a week intravenously.

Excretion.—About 50 p.c. of the metal is eliminated by the kidneys and partly by the intestine. Part is retained in the liver and muscle for a long time.

Mode of administration.—The usual dose of sanocrysin for Indian patients is smaller, and the initial course should be as follows, viz.—0·05, 0.1, 0.2, 0.3, 0.5, 0.65, 0.75 and 1.0 grm. The maximum dose is seldom required. The optimum dose should be repeated till a total of 4 to 5 gm. has been given. In weak and febrile patients it is better to begin with 0·025 to 0.05 gm. ($\frac{3}{8}$ to $\frac{1}{3}$ gr.). The usual method of administration is the intravenous route, once a week, and a 5 p.c. solution being almost isotonic with blood should be used. For intramuscular injection a 3 p.c. solution in sterile water, or a 5 p.c. oily suspension is preferable, as this is less liable to cause local irritation. An all-glass syringe with a platinum needle should be used as the drug acts on steel. The injection should be given in the morning by choice and the patient kept in bed during the course of treatment. Examine the urine daily for albumin and cast and make a note of the temperature for any febrile reaction. It should never be given subcutaneously.

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Indications for the use of sanocrysin have been summarised by G. Gregory Kayne as follows :—*

(1) *Recent lesions* (i.e., those associated with symptoms of not more than three to four months' duration) *of the exudative type* (showing fluffy-edged soft X-ray shadows). When cavitation is present it may be used, but artificial pneumothorax should be done.

(2) *Recent exudative lesion occurring in association with old standing disease.*

(3) In patients in whom suggestive shadows are found in routine examinations in the absence of definite clinical evidence of activity.

Solganal.—Di-sodium salt of 2-sulphomethlylamino-2-auromercaptobenzol-1-sulphonic acid. Contains 36·5 p.c. of gold. In *tuberculosis. Dose.*—0·005 to 0·5 grm. *intravenously* to be given once or twice a week according to reaction. The dose to be cautiously increased.

Solganal-B is aurothioglucose, for *intramuscular and subcutaneous use.* The initial dose for Indian patients should not be more than one-fourth of the minimum dose recommended, and if this is not followed by any febrile reaction then the dose may be increased by the same amount with each subsequent injection. Unless the dose is carefully regulated it may cause severe reaction and make the condition worse. *Dose.*—0·005 to 0·5 grm.

Depilatory

Thallium

THALLII ACETAS.—Prepared by neutralising an aqueous solution of Thallous Hydroxide with acetic acid. In colourless needles, or in white crystalline powder, soluble in water.

Dose.—0.008 grm. per kilogram of body weight (or $^2/_{35}$ gr. per pound).

Action and Uses

Thallium salts produce no immediate effects on animals beyond causing some relaxation of the plain muscles, but a few days later (generally a fortnight) causes shedding of the hair in all animals. Its chief use is as a **depilatory** in cases of ringworm of the scalp, when the hair becomes brittle in a week's time and falls off within the next week, and the hair starts to grow in about the same time. It is generally administered in tablets or sweetened aqueous solution, and since children tolerate it better its use is confined to children under ten years of age. As a rule one dose is sufficient and the drug is not repeated within a period of three months.

Since the drug is apt to produce toxic symptoms it should be used with extreme caution, and the dose should be well regulated. Large doses will cause shedding of hair from all parts of the body innervated by the sympathetic. Toxic symptoms are vomiting, diarrhœa, stomatitis, albuminuria, joint pains confined to lower limbs, peripheral neuritis, delirium and collapse. Remember that the *margin of safety* between the epilation dose and the toxic dose is very low, and it should not be used when there is albuminuria or any general constitutional disease.

Treatment of poisoning.—Stomach wash or an emetic followed by a purgative. In acute cases dextrose intravenously. Caffeine or adrenaline to overcome shock, and sodium iodide (5 to 15 grs. daily) to convert the toxic soluble thallium salts into almost insoluble iodides. Sodium thiosulphate (5 to 15 grs. daily) intravenously to promote gradual elimination. Children should receive proportionately smaller doses.

* Proceedings of the Royal Society of Medicine, Vol. xxviii, No. 11.

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GROUP IV: METALLOIDS

Bismuth, Arsenic, Antimony, Chromium, Phosphorus

Bismuth, Arsenic and **Antimony** will be discussed with other Chemotherapeutic Agents.

CHROMII TRIOXIDUM

Chromium Trioxide

Syn.—Acidum Chromicum ; Chromic Anhydride.

Source.—Obtained by the interaction of sulphuric acid and potassium dichromate.

Characters.—Dark red, acicular crystals, or dark brown masses. No odour, deliquescent and corrosive. *Freely soluble* in water and ether.

N.B.—Liable to cause combustion or explosion when in contact with alcohol, ether, glycerin and other organic substances.

Pharmacology

Externally.—It is a powerful **oxidising agent**, destroying the lower organisms, and is therefore a **deodorant** and **disinfectant.** It is powerfully hygroscopic and takes up water from moist tissues and oxidises organic substances, and acts as a **caustic.**

Therapeutics

Externally.—Liquor acidi chromici (25 p.c. solution) is used for destroying **warts.** It should be applied with a pointed glass rod, the adjacent parts being protected by a plaster or ointment, and a piece of wet lint kept ready to absorb any superfluous acid. A weak lotion (1 in 40 or more) is useful for **ulcerated gums** and **foul sores.** A 3 per cent. solution checks perspiration of the feet.

Chromic acid solution does not burn or stain linen, and is a delicate test for albumin in the urine.

PHOSPHORUS

Phosphorus. (Not Official)

Source.—A solid non-metallic element, obtained from calcium phosphate.

Characters.—A semi-transparent, wax-like solid, emitting white vapours and is luminous in the dark ; ignites in the air. *Solubility.*—Insoluble in water ; soluble 1 in 25 of chloroform, 1 in 350 of alcohol (90 p.c.), 1 in 80 of olive oil and of ether ; 2 in 1 of carbon disulphide, 1 in 60 of oil of turpentine.

Dose.—1/100 to 1/25 gr. or 0.0006 to 0.0025 grm.

Non-official Preparations

1. **Pilula Phosphori.**—Each pill contains 1/100 gr. of phosphorus. *Dose.*—1 to 4 pills.
2. **Liquor Phosphori Co., B.P.C.** *Syn.—Tr. Phosphori Co.*—Phosphorus 2 grm., chloroform 175 mil., dehydrated alcohol to 1000 mil. *Dose.*—3 to 12 ms. or 0.2 to 0.8 mil.
3. **Calcii Hypophosphis.**—A white, crystalline pearly salt. Taste, bitter, nauseous. Soluble 1 in 8 of water. *Dose.*—3 to 10 grs. or 0.2 to 0.6 G.
4. **Syrupus Calcii Hypophosphitis, B.P.C.**—Calcium hypophosphite 18.3 grm., hypophosphorous acid 2.5 mil., sucrose 800 grm., water to 1000 mils. *Dose.*—1 to 4 drs. or 4 to 16 mils.
5. **Calcii Glycerophosphas, U.S.P.**—A calcium salt of glycerophosphoric acid. A fine, white, hygroscopic odourless powder. *Dose, U.S.P.*—0.3 gm. or 5 grs.
6. **Ferri Glycerophosphas.**—*Dose.*—1 to 5 grs. or 0·06 to 0·3 G.
7. **Sodii Glycerophosphas.**—*Dose.*—5 to 10 grs. or 0·3 to 0·6 G.

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8. **Syrupus Glycerophosphatum Compositus, B.P.C.**—Calcium glycerophosphate, solution of potassium glycerophosphate and solution of sodium glycerophosphate, each 22.9 grm., magnesium glycerophosphate 11.4 grm., iron glycerophosphate 5.7 grm., potassium citrate 11.4 grm., glycerophosphoric acid 20.8 mil., caffeine 5.7 grm., strychnine 0.2 grm., glycerin 200 mils, sucrose 400 grm., solution of Bordeaux B 31.2 mil., chloroform 2.1 mil., alcohol (90 p.c.) 4.2 mil., water to 1000 mil. Contains 1/60 gr. of strychnine in 1 dr. *Dose.*—1 to 2 drs. or 4 to 8 mils.

Pharmacology

Phosphorus is an important constituent of the body and forms about 0.7 p.c. of the body weight. It exists in the bone as phosphate of calcium and magnesium, and as soluble phosphate ions in the blood and other fluids, and as nuclein, lecithin and phosphatides in the tissues and plasma. As a therapeutic agent its value is limited, although it has a specially interesting physiological action. As a poison it is important.

Stomach and liver.—In moderate doses it causes **nausea** and **vomiting.** The epithelial cells of the stomach and intestine undergo fatty changes giving rise to abdominal pain, vomiting and diarrhœa, the vomited matter having a garlic odour. These symptoms *do not appear immediately after administration, but are delayed for hours and days.* The liver is affected early causing fatty changes, and becomes enlarged, painful and tender. Jaundice is a marked symptom and is due to the cells being infiltrated with fat which press on the bile capillaries and occlude them.

Blood.—Phosphorus is absorbed in the small intestine and circulates as such. In therapeutic doses it increases the number of red blood corpuscles, although it was formerly believed to have a destructive action on the red blood cells. It has however no such action even in severe poisoning. It retards coagulation of the blood due to destruction of fibrinogen or fibrin ferment, or to the formation of peptone bodies from protein destruction. This factor and the fatty degeneration of the endothelial tissue of the capillaries account for hæmorrhage in poisoning.

Bones.—When continued long in such minute doses as not to affect the stomach or liver, it has a specific action on the bone. There is an increased osseous deposit and the long bones become more dense at the expense of the cancellous tissue. Instead of the porous bone tissue filled with red marrow there develops from the epiphysis line a dense, hard substance of the same nature as that forms on the outer shell on the diaphysis. Phosphorus therefore stimulates growth of bones, *i.e.*, there is an excess of anabolic over the katabolic processes in the metabolism of bony tissue. The bone-marrow in chronic poisoning becomes hyperæmic, the fat cells disappear and the leucoblastic cells increase.

Metabolism.—In small doses continued long phosphorus stimulates metabolic processes and helps growth and formation of new tissue. The destructive effects are observed in chronic poisoning, or as a secondary process after a single large dose. The main symptoms are characterised by increased tissue destruction with disturbances of synthesis, oxidation and dissociation. Less fat but more carbohydrate and protein are broken up, though imperfectly, and the excretion of nitrogenous metabolites, *viz.*, amino acids, leucin, tyrosin and peptone like bodies is increased. The excretion of urea is not increased, on the contrary may be diminished, but there is an excess of ammonia which enters the blood to neutralise acidosis formed by the production of lactic acid and other organic acids as a result of incomplete oxidation of fat, glycogen, etc. The respiratory interchange is diminished and oxygen consumption and carbonic acid excretion is reduced. The cause of this diminished oxygen intake is not definitely settled, although it has been suggested that phosphorus renders the cells less capable of utilising oxygen.

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Fatty infiltration occurs in almost all organs of the body, that of the liver being most extensive. Another important effect is the change in the carbohydrate metabolism with disappearance of glycogen from the liver. The increased excretion of nitrogen has been regarded as the result of this effect since the body draws on the protein to make up the deficiency of the carbohydrate. Moreover, the emptiness of glycogen of the liver leads to mobilisation of the fats to supply the want, and since the liver cannot utilise the fat completely it is deposited in the cells of this organ.

Absorption and elimination.—Absorption is slow and occurs from the intestine, and to some extent by the lungs when inhaled. The systemic effects are therefore delayed several days. As it is soluble in oily substances, presence of oil and fats in the intestine favours absorption. A portion is oxidised to phosphoric acid and some phosphorus is excreted by the lungs and urine.

Acute toxic action.—Acute poisoning may occur from swallowing rat-paste or lucifer match-heads. Besides gastro-enteritis already described, there is considerable prostration and occasionally collapse and death. Generally these symptoms come on in a mild form, and the patient does well for a few days. Then, after an interval, jaundice is noticed, with a tender, enlarged liver. The jaundice soon deepens; vomiting, which may be luminous, and purging of dark-coloured blood set in; temperature first rises and then falls; the pulse becomes weak and rapid; the skin cold and clammy; and the urine scanty, high-coloured, and albuminous. Muscular twitchings, convulsions or coma supervene, terminating in death. Abortion frequently follows possibly due to degeneration of the blood vessels. **Fatty degeneration of the liver,** with general ecchymosis and hæmorrhages are the common P.M. apearances.

Antidotes.—Stomach-pump, or emetics; copper sulphate is the appropriate emetic. It should be given in 3 gr. doses every 10 minutes till vomiting takes place, and then 1 gr. every quarter of an hour as an antidote as it oxidises the phosphorus and envelops the globules with a coating of reduced copper which retards absorption. The stomach should be washed out with a 0.2 p.c. solution of potassium permanganate which converts phosphorus into phosphoric acid. If rejected, give it with morphine solution (10 ms.). Ozonized oil of turpentine was used formerly but has been found to be of no value. Alkalies may be given afterwards to neutralise acidosis, and demulcent drinks. Avoid fats, butter and oils which dissolve phosphorus.

Chronic toxic action.—Chronic poisoning is rare, *and occurs only in those workmen who are exposed to the fumes* of phosphorus. Gastro-enteritis, fatty degeneration, **necrosis of the jaw,** general tuberculosis are the prominent symptoms. Phosphorus fumes attack the bone through carious teeth or spongy gums, but this effect is not produced by its internal use.

Therapeutics

As a nervine tonic, the hypophosphites and the glycerophosphates have been given in **nervous exhaustion, over-taxation of the brain** from prolonged strain and overwork, but as they pass unchanged through the system and can be almost entirely recovered from the urine, they can furnish no phosphorus to the nerve tissue. They are used largely in wasting diseases like **phthisis,** and in **chronic bronchitis,** but with doubtful results. Phosphorus has been given in affections dependent on malnutrition, such as **anæmia, leucocythæmia,** with occasional success. Dr. Kussowitz, obtained very good results in the **rickets** of children, the dose being $\frac{1}{120}$ to $\frac{1}{60}$ gr. *per diem* for a child weighing 12 lbs. It is no doubt useful in **ununited fractures,** specially during pregnancy, and in **osteomalacia.** But the use of phosphorus in these conditions has been given up in favour of codliver oil, vitamin D, ultra-violet rays, and sunlight.

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GROUP V

DRUGS ACTING ON THE NERVOUS SYSTEM

By the nervous system we mean the brain, the bulb, the cord, the nerves, both sensory and motor, and the various ganglia. The highest motor and sensory centres as well as those of volition, intellect, emotion, etc., are contained in the cerebral convolutions, while the simple automatic and reflex centres are in the basal ganglia, cerebellum, medulla and cord. All nerve centres are connected with one another by nerve filaments called *collaterals*, for co-ordination of impulses, and constitute the central nervous system. The cerebral or highest centres are not only excitable or capable of being brought into action by afferent impulses, but possess an inherent power of spontaneously originating impulses themselves. Their action is therefore both *reflective* and *spontaneous*. To the pharmacologist this reflective or *reflex action* is important. It is effected by (1) an afferent sensory nerve; (2) reflex centre; and (3) an efferent motor, or secretory nerve. An impression excited by an irritant on the skin or other structures of the body is conducted through an afferent nerve *via* the posterior root ganglion, to the spinal cord, where it produces certain protoplasmic disturbance, resulting in a force, which either remains there as potential energy, or is conveyed by a different tract—efferent nerve—to perform some specific action either in the muscle, viscera, or the blood vessels. This process is spoken of as reflex action. This sensory stimulus instead of being reflected from the cord may be conveyed by the sensory tracts to the sensory area of the brain, where it will be perceived as an impression either of pain, heat or cold, and so forth, to be felt at the seat of stimulus, and then lead to volitional conveyance of impulse in the form of movement, etc. It will be observed that although the stimulus originates in the skin or other structures, it is perceived as a sensation in the brain. Thus an impression which is peripheral in origin becomes a sensation which is cerebral, and the result may or may not be volitional.

In considering the action of drugs on the nervous system we find that some affect one centre, while others another; a few influence the lower centres only; others centres for emotion and intelligence; and lastly some alter the nervous mechanism of different viscera.

Drugs acting on the nervous system may be classified as follows:—

Class A: Drugs acting on the brain]

1. Intoxicant: **Alcohol**
2. General anæsthetics and narcotics: **Chloroform, Ether, Ethylene, Nitrous Oxide, Ethyl Chloride**

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3. Hypnotics and narcotics: **Opium, Cannabis Indica, Bromides, Chloral Hydras, Chlorbutol, Butyl-chloral Hydras, Paraldehyde, Sulphonal, Methylsulphonal, Barbitone, Soluble Barbitone, Carbromalum, Phenobarbitone, Soluble Phenobarbitone, Nembutal, Amytal, Sodium Amytal, Evipan, Sodium Evipan, Urethane, Hyoscine Hydrobromide**

Class B: Drugs acting on the cord
1. Convulsant: **Strychnine**

Class C: Drugs acting on the autonomic system
1. Drugs stimulating the parasympathetic endings: **Pilocarpine, Physostigmine, Acetyl-choline, Muscarine**
2. Drugs depressing the parasympathetic endings **Belladonna, Hyoscyamus, Stramonium**
3. Drugs stimulating the sympathetic endings **Adrenaline, Ephedrine, Tyramine**
4. Drugs depressing the sympathetic endings: **Ergotoxine, Ergotamine, Apocodeine**

Class D: Drugs acting on the motor nerve-endings and the ganglia' **Curare, Nicotine, Gelsemium, Conium, Lobeline**

Class E: Drugs depressing the sensory nerve-endings **Cocaine, Procaine Hydrochloride, Orthocaine, Benzocaine, Amylocaine Hydrochloride, Hydrocyanic Acid, Urea Quinine**

Class F: Drugs stimulating the sensory nerve-endings *See* **Counter-irritants**

Class A: Drugs acting on the Brain

The structure of the brain being more complicated, our knowledge of the pharmacology of this organ is obscure. Although we can influence the functions of the brain more rapidly, yet we cannot localise the action of drugs, nor the exact manner by which they produce the different symptoms. It has, however, been found that they follow certain laws while acting on the brain; they are:—

(*a*) *The law of dissolution.*—This was first described by Jackson, and consists of the progressive action of a drug on the nerve centres in the reverse order of their development in animal life, *i.e.*, those that are the highest and developed last are affected first, and then the next to highest, and so on, until the lowest ones are affected. Thus alcohol paralyses the highest centres as will, intellect, etc., then those of the muscles, as is evidenced by staggering gait, and lastly those of the heart and respiration.

(*b*) *The law of primary stimulation and subsequent depression.*—This is well illustrated by the action of a drug which in small doses stimulates certain functions, and in large doses depresses them, *e.g.*, chloroform.

The different nerve cells react differently to drugs. Thus the functional activity of the brain is influenced by a special group of drugs, of these some like caffeine, atropine, camphor, cocaine, alcohol, chloroform, etc., excite the brain and are called **cerebral stimulants.** In certain instances the excitement is of a disorderly nature accompanied by incoherence and delirium, and the drugs so acting are known as *deliriants*; while others produce mirthful and comfortable feelings, when

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they are called *exhilarants*. Another set of drugs depress the activity of the brain and are known under different names according to the nature of their action, viz.—**hypnotics, narcotics, general anæsthetics**. Alcohol, ether and chloroform produce a certain amount of excitement at the beginning, and subsequently according to the quantity used, alcohol produces *intoxication and narcosis*, chloroform and ether produce *loss of consciousness with general anæsthesia*; and opium, cannabis indica, chloral hydras, etc., act as *hypnotics or narcotics*.

Another group of drugs produce very little effect on the brain but influence the activities of the spinal cord or the different nerve-endings. Others again show a selective action on certain parts of the central nervous system. For instance, morphine while stimulating the cardiac vagus centre depresses the respiratory centre; apomorphine acts chiefly on the vomiting centre; caffeine and cocaine stimulate the psychic centre; atropine and camphor the motor centre; and quite a large number of drugs act on the vital medullary centres.

1. Intoxicant

ALCOHOL DEHYDRATUM

Dehydrated Alcohol

Syn.—Absolute Alcohol; Dehydrated Ethanol, U.S.P.

Source.—Obtained by the removal of water from alcohol (95 p.c.), and subsequent distillation. Sp. gr. 0.7936 to 0.7967. Contains not less than 99·4 p.c. v/v or 99 p.c. w/w of C_2H_6O.

ALCOHOL

Alcohol (95 p.c.)

Source.—A mixture of ethyl alcohol and water, obtained by the distillation of fermented saccharine liquids.

Characters.—A colourless, transparent, mobile and volatile liquid, with a characteristic spirituous odour. Taste, burning. Burns with a blue smokeless flame.

SPIRITUS METHYLATUS INDUSTRIALIS

Industrial Methylated Spirit

Source.—A mixture made by a legally authorised methylator, of 19 volumes alcohol (95 p.c.) with 1 volume of approved wood naphtha, and is of the quality known as '66 O.P. Industrial Methylated Spirits.'

Characters.—Similar to those of alcohol (95 p.c.), but having in addition the odour of wood naphtha.

Official Diluted Alcohols

1. **Alcohol** (90 p.c.). *Syn.—Rectified Spirit.*—Dilute 948 mils of alcohol (95 p.c.) to one litre with distilled water.
2. **Alcohol** (80 p.c.).—Dilute 842 mils of alcohol (95 p.c.) to one litre with dislilled water.
3. **Alcohol** (70 p.c.).—Dilute 737 mils of alcohol (95 p.c.) to one litre with distilled water.
4. **Alcohol** (60 p.c.).—Dilute 632 mils of alcohol (95 p.c.) to one litre with distilled water.

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5. **Alcohol** (50 p.c.).—Dilute 526 mils of alcohol (95 p.c.) to one litre with distilled water.
6. **Alcohol** (45 p.c.).—Dilute 474 mils of alcohol (95 p.c.) to one litre with distilled water.
7. **Alcohol** (25 p.c.).—Dilute 263 mils of alcohol (95 p.c.) to one litre with distilled water.
8. **Alcohol** (20 p.c.).—Dilute 210 mils of alcohol (95 p.c.) to one litre with distilled water.

Note.—On mixing alcohol and water contraction of volume and rise of temperature occur.

The following is the list of wines, showing the amount of absolute alcohol by weight:—

Spiritus Frumenti (Whisky) 51 to 59 p.c.
Rum, Gin, and strong Liqueurs, about 51 to 59 p.c.
Sherry, Port, Madeira, about 16 to 30 p.c.
Champagne, about 10 to 13 p.c.
Hocks, Burgundy, about 9 to 13 p.c.
Spiritus Vini Gallici (Brandy) 43 to 57 p.c.
Spiritus Vini Rubri (Port), 20 to 30 p.c.
Claret, 8 to 12 p.c.
Ale and Porter, about 3 to 5 p.c.
Cider, 5 to 9 p.c.
Beer, 2 to 5 p.c.
Kounniss and Ginger Beer, about 1 to 3 p.c.

Pharmacology of Alcohol

Externally.—Alcohol has a great affinity for water, it **coagulates protein** and irritates and **destroys cells.** It is therefore a **protoplasmic poison.** It is an **antiseptic,** and it has been found that in the preparation of alcoholic liquors the activity of yeast is retarded when the strength of alcohol reaches 10 p.c. and completely stopped when it reaches 15 p.c. When applied to the skin it evaporates quickly producing a sensation of cold which is more marked when used diluted with water. On the other hand if the evaporation is checked, or if it is rubbed in, it abstracts water from the skin and renders the skin drier and harder. When applied in sufficient concentration (60 to 80 p.c.) it **dilates** the local **blood vessels,** produces a feeling of warmth, and renders the skin red, thus acting as a **local rubefacient** and **counter-irritant.**

Internally.—Undiluted alcohol has the same action on the mouth as on the skin, *viz.*, it coagulates the protein and abstracts water and acts as a local irritant. It stimulates the nerves of taste and causes a **reflex flow of saliva,** and excites the **psychic secretion of gastric juice.**

Stomach and intestine.—The action of alcohol on the stomach may be considered from three points of view: (*a*) its chemical effect on the stomach contents, (*b*) its effects on the stomach functions, and (*c*) its effects on the coats of the stomach. While it is true that undiluted whisky or brandy will precipitate proteins of food and possibly pepsin, and also interfere with the process of digestion, moderate quantities of diluted alcohol have only a negligible action on the

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chemical process of digestion. Wines and malt liqueurs, owing to the presence of organic acids and colloidal constituents, if taken in large quantities have a deleterious effect on digestion. In the same way red wines, owing to the presence of tannin, retard digestive process more than white wines by precipitating proteins.

In weak solutions, *i.e.*, below the strength of 10 p.c., alcohol has practically no effect on the stomach wall beyond dilating the vessels and causing a sense of warmth, but in large and repeated doses, or in concentrated solutions, it irritates the mucous membrane, increases the secretion of mucus, and retards the secretion of gastric juice. If this process is continued over long periods, as in chronic alcoholics, **gastric follicles atrophy** and **dyspepsia** becomes permanent.

In moderate strengths and taken with food or after food, it tends to **promote digestion** by direct simulation of the fundus of the stomach, causing an abundant secretion of gastric juice. If taken with bitters before food it increases the appetite juice, although a small quantity will often produce manifestations of intoxication. As regards motor activity and secretion, alcohol in weak solutions (10 p.c.) has very little effect if any.

A moderate dose of strong alcohol, *e.g.*, whisky or brandy, on reaching the stomach, at once **reflexly stimulates** the heart, raises the blood pressure, quickens the pulse and increases the respiratory movements. Since it causes dilatation of the vessels, specially of the skin and increases the functional activity of different organs, alcohol is regarded as a general stimulant. But, as will be seen later, these effects are not dependent upon a direct stimulation of the nerve centres, but are purely reflex phenomena and indirect result of inco-ordination. Irritation of the mucous membrane, emotional excitement and increased movement are responsible for the acceleration of the heart.

In the intestine alcohol is so much diluted by the time it passes the pylorus that it exerts very little effect there. After an excessive amount some reaches the duodenum and acts as an irritant. Brandy has a reputation among the lay public as an astringent in diarrhœa. Owing to increased formation of secretin pancreatic secretion is very largely increased whether alcohol is given by the mouth or per rectum.

Liver.—After absorption alcohol passes directly to the liver through the portal circulation, where it affects the hepatic cells producing inflammation. It may dsappear in a few days if no more alcohol is taken, but if long continued, it establishes permanent changes in the liver leading to **cirrhosis or fatty degeneration,** or both. Moderate amounts as a rule are sufficiently diluted by the portal blood, but excessive drinking surcharge the portal blood with alcohol.

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Food value of alcohol.—The question whether alcohol is a food has been much discussed, and the chief point is whether it can be regarded as a protein sparer. Proteins contribute to the formation and repair of tissues ; carbohydrates and fats are sources of heat and energy. Since alcohol does not contain any nitrogen, it cannot replace protein and therefore has no power to build tissues. Since about 90 p.c. of alcohol taken disappears in the body and is converted into CO_2 and water, alcohol by virtue of the chemical energy thus liberated can replace carbohydrates and fats in the diet, and in this sense is a **non-nitrogenous food.** Moreover it does not require more energy for absorption than other foods. But when taken with other foods it economises the use of fat and carbohydrate, which in their turn are stored in the body, the carbohydrate as glycogen, and fat in the tissues. As alcohol does not require digestion it is in a sense superior to other foods.

Although it cannot replace protein, alcohol will, under certain conditions, spare the protein in the same way as fat. It has been experimentally shown (Rosemann and Neumann) that on an ordinary diet the nitrogen equilibrium is maintained at a constant level, but if part of fat is withheld from the same diet, nitrogen excretion increases, showing destruction of protein, *i.e.*, proteins are being drawn upon to supply the energy required in place of fat. If, however, an amount of alcohol chemically equivalent to the omitted fat is added to the diet, nitrogen equilibrium again becomes established. It is thus evident that alcohol is able to spare protein in the same way as the fat, and can thus prevent tissue waste. Alcohol therefore may be regarded as a food in the sense that it will, when given with other foods, replace carbohydrate and fat for a short time and would supply energy and spare protein and prevent tissue waste. But the value of alcohol as a food is limited because the supply of energy is fixed and cannot be adjusted according to the needs of the body, nor can it be increased to meet sudden emergency, because it cannot be stored in the body like fat or carbohydrate as reserve.

Nervous system.—In moderate doses, the action of alcohol on the nervous system is that of **apparent stimulation** which is soon followed, according to the quantity used, by that of **sleep** and **coma.** In small doses it produces a feeling of mental and physical well-being. Imagination becomes brighter, feelings elevated, intellect clearer (highest functions of the brain), senses more acute, bodily activity more predominant, and some of the lower appetites sharpened. If the dose is increased, judgment fails while the imagination, emotion, and power of speech are still excited, then the imagination and will power give way. If indulgence is continued further, symptoms of acute alcohol poisoning

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appear so that he loses his mental balance. He talks, laughs, sings or cries without restraint, but gradually he loses control over these functions also, and his speech becomes thick, incoherent and at last suspended. His muscles next get affected, at first the delicate movements, such as writing, playing on the piano, etc., are abolished. But if the dose is very large there is complete insensibility, narcosis, muscular relaxation with involuntary passage of urine and stool and subnormal temperature. The breathing becomes stertorous with cyanosis, finally the patient dies from respiratory paralysis. It will be seen that in its progressive action either of stimulation or of depression it follows the law of dissolution (*see* page 135). But the explanation of these effects is not very clear. Binz and his followers maintain that it first stimulates the nerve cells in the central nervous system and subsequently depresses them, and we have already noticed that alcohol in small doses stimulates the higher functions of the brain which functions are subsequently depressed by larger doses. The other view is that of Schmiedeberg. He holds that alcohol acts as a narcotic from the very commencement and the symptoms of stimulation are the effect of the depressant action on certain higher cerebral functions which normally exert a controlling influence, *viz.*, the will and self-restraint. This latter view seems to have more supporters and is generally accepted.

Observations have shown that when alcohol is taken without any exhilarating company many of the manifestations are not elicited. In fact the effects depend upon the nature of the environment and on the inherent mentality of the individual, and would produce quite diverse symptoms on different persons and different effects on the same individual under different conditions. Owing to a certain degree of freedom from restraint, the person will be talkative, boisterous sentimental or melancholic according to the individual peculiarities.

Circulation.—The reflex effect of alcohol in stimulating the circulation and respiration has already been mentioned. But its action after absorption is uncertain and depends on several factors, viz. the dose and concentration, the mode of administration and the condition of the individual. After absorption the vessels of the skin dilate giving rise to a feeling of warmth but those of the internal organs, specially of the splanchnic area, constrict so that it allows more blood to pass through the vital organs, chiefly the heart and the central nervous system, and causes a **rise of blood pressure.** The normal heart muscle is not affected in small doses, but when exhausted it may be stimulated. During the stage of intoxication the pulse is accelerated due to excitement. The output of the heart, the force and amplitude of the pulse, and the circulation in general are more or less improved.

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When large doses are taken, the stimulant effect is followed by depression with fall of pressure due to dilatation of the splanchnic vessels replacing the constriction of the first stage. It should be noted that the heart which is stimulated at first is more exhausted than before after the temporary effect has passed off. Large doses do not stimulate the heart at all, in fact the heart is paralysed both reflexly and after absorption.

Respiration.—We have already observed that the medullary centres are affected last, in fact, respiration, though it becomes stertorous, does not stop even after the patient has become completely unconscious and all the reflexes are abolished. The respiratory centre is stimulated reflexly from the stomach before absorption however, but whether the centre is stimulated after absorption has been the subject of much controversy, and it is generally agreed that although the centre is not stimulated to any marked degree in small doses it is not depressed except after large doses and that even as a late symptom of poisoning. In fevers and diseases of the lungs like pneumonia, the respiration is slowed and steadied not from any direct action on the centre but through its narcotic effect it lessens excitability and anxiety and appreciation of distress.

Muscular system.—It was formerly believed that alcohol increases the physical power for more work, but later observations have shown that it is not so, although in the beginning the muscular strength increases through increased circulation in the nervous system. This is soon followed by diminution of working power, so that the total amount of work done is less.

Alcohol is taken not for any stimulant effect, but after severe muscular work for its depressing effect on the nervous system, which gives a feeling of comfort and well-being while forgetting fatigue. In fact observations made with ergograph have shown that muscular work is not increased but it lessens the appreciation of fatigue so that the workers think that they have done more work, or perhaps owing to this fact may do more work, not from increased capacity but from lessened appreciation of tiredness.

Skin and kidneys.—Alcohol is a **mild diaphoretic** due partly to the dilatation of the skin vessels and partly to its effect on the sweat glands. This dilatation gives rise to a feeling of comfort and heat. Alcohol therefore is a mild **antipyretic** and for this purpose is used to promote sweating after an exposure to cold to avert the onset of catarrhal infection. But the diaphoresis depends on the renal excretion and in cold climates instead of diaphoresis there is **diuresis,** and the large quantity of water taken with alcohol is excreted by the kidneys. There is also some dilatation of the renal vessels. If alcohol is taken in large amounts a

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portion is excreted in the urine unchanged. Gin has a greater diuretic effect than other spirits. Prolonged use produces changes in the renal cells and may give rise to chronic nephritis.

It should however be noted that after very large quantities of alcohol the dilatation of the cutaneous vessels may proceed to such an extent that death may follow from excessive radiation of heat, though the drinker may feel a sense of temporary warmth in the beginning, if his vessels were contracted previously from cold air.

Temperature.—Alcohol acts as a mild **antipyretic**, by increasing the heat loss (*a*) from dilatation of the cutaneous blood vessels thereby producing increased perspiration and radiation, although it causes a subjective feeling of warmth; and in larger doses (*b*) by acting on the heat regulating centre which is rendered less sensitive. It is therefore harmful to take alcohol during exposure to cold, for although there is a subjective sensation of warmth it lessens the power of the body to conserve heat.

Absorption and elimination.—Taken by the mouth about 25 p.c. is absorbed by the stomach, the rest is passed into the intestine to be completely absorbed and no alcohol reaches the colon. It is broken down entirely in the body, only from 2 to 10 p.c. being excreted by the breath, skin and urine. Mellanby has shown that it appears in the blood within five minutes after administration by the mouth, and that it reaches highest concentration within an hour and a half. It is generally believed that a concentration of 0.2 to 0.4 p.c. in the blood or urine implies moderate intoxication, over 0.4 p.c. marked intoxication in most, and over 0.5 p.c. in all. The concentration of alcohol in the blood of living animals in deep narcosis is 0.7 p.c.

Acute toxic action.—When an excessively large dose is taken the stage of stimulation is soon followed by that of narcosis with impairment of sensation and motion, etc., already described under nervous system. Death is relatively rare, but may occur suddenly from reflex stoppage of the heart, or the coma may become deeper and death may occur from paralysis of respiration or the heart, or from pulmonary œdema, generally within twentyfour hours. If coma continues for more than twelve hours recovery is exceptional.

Treatment.—Evacuate the stomach by pump or emetics, such as apomorphine. If the patient cannot swallow, coffee with ammonia may be introduced with the pump after stomach washing. Amyl nitrite inhalation, strychnine subcutaneously or caffeine. Subsequent headache and nervousness require bromides, feeling of depression and gastritis should be treated with bicarbonate of soda, sal volatile and tr. capsicum.

Chronic toxic action or "Alcoholism" is induced by prolonged alcoholic indulgence. Insomnia, muscular tremor, and gastric disturbance are the early symptoms. Gastritis, peripheral or multiple neuritis, cirrhosis of the liver causing ascites, chronic interstitial nephritis causing anasarca, dilatation of the heart, gout, nervous disorders, such as delirium tremens, epilepsy, paralysis, insanity, etc., are the diseases which afflict confirmed drunkards. Chronic

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alcoholics exhibit a train of symptoms which are grouped under the heading of *Karsakoff's Psychosis*, in which emotional tendencies, untruthfulness, indiscretion, mental confusion with loss of memory for recent events, and loss of idea of space and time are often present. Generally they are thin, but a few, especially those who drink beer, get fat. They cannot withstand well any serious illness, such as pneumonia, and are particularly liable to attacks of phthisis. Gin drinkers mostly suffer from cirrhosis of the kidneys and liver.

Therapeutics of Alcohol

Externally.—Application of an alcoholic lotion with a piece of cloth and allowing free evaporation, is useful in some forms of **headache, acute inflammation,** as sprains, bruises, etc., and prevents bed sores and cracked nipples by hardening the skin. Sponging with alcoholic lotion relieves **itching of urticaria.** Pure alcohol or brandy when rubbed into the body checks excessive perspiration and brings back warmth to the surface in collapse and syncope. Liniments containing alcohol are used as counter-irritants in **stiff joints, chronic rheumatism, bronchitis, pneumonia,** etc. Absolute alcohol is sometimes injected into nerves in cases of **sciatica** and **neuralgias,** when it relieves the pain by causing degeneration of the particular nerve, and the pain does not recur till the nerve has regenerated again, which takes several months.

Alcohol (70 p.c.) is used for washing the skin and the hands before operation, for **sterilising** delicate instruments, and syringe for hypodermic injection. Concentrations above 80 p.c. and below 60 p.c. are almost inactive since they do not penetrate proteins of bacteria readily.

Internally. **Mouth.**—As a **local astringent, anodyne** and **antiseptic,** it is used in many mouth and throat diseases. Undiluted brandy held in the mouth relieves **toothache** and the pain of **follicular tonsillitis.** The latter disease is also benefited by its astringent and antiseptic properties.

Stomach.—As a **digestive stimulant,** alcohol may be given in small doses just before or during meals in the following class of cases:—

1. Convalescents from acute illness with weakened appetite and digestion.
2. Patients suffering from chronic wasting diseases.
3. Town-dwellers leading a sedentary life.
4. Old and overworked persons.

A good peg of whisky or brandy with hot water often relieves **gastric spasms. Fainting, syncope,** or **threatening collapse** may be averted by a single large dose of brandy or whisky by reflexly stimulating the circulation. **Diarrhœa** or **cholera** in the beginning may be checked by a stiff dose of brandy.

Heart.—As a **cardiac stimulant,** brandy or whisky is used in threatening **cardiac failure** due to shock, hæmorrhage, febrile and other diseases. Its value in shock is doubted by

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many careful observers; although it is possible that it benefits by lessening anxiety and pain provided the patient is conscious. As a diffusible stimulant it acts purely reflexly, by increasing the pulse-rate, blood-pressure and the respiration. This effect being of short duration it is used mainly as an emergency drug. The narcotic effect is also of value, since the psychic centres are not so easily excited and the medullary centres are less subject to dangerous shock.

Nervous system.—Alcohol must be used with great caution in depressed conditions of the nervous system lest a bad habit be induced. Most nervous diseases do not require any alcohol. In some cases of **insomnia, hysteria** and **neuralgia,** alcohol no doubt affords temporary relief, but it must, if possible, be avoided for fear of generating intemperance. As to the use of alcohol in **acute alcoholism** (delirium tremens), opinions differ. It is entirely withdrawn in the course of a few days. A sudden stoppage will precipitate the onset of delirium tremens. As a hypnotic alcohol may be used at bed-time as an adjuvant to other simple hypnotics.

Kidneys.—Gin is a powerful diuretic, because it contains juniper which is also a diuretic. As alcohol is eliminated by the kidneys, and is an irritant to the mucous membrane of the urethra, it should be avoided in **gonorrhœa, gleet,** etc.

Fevers.—Alcohol was formerly almost invariably used in acute febrile diseases as a respiratory and circulatory stimulant, but its use has become very limited in recent years, in fact most cases of fevers do well without it. Experience alone will guide the practitioner when and where to use wines. It is only in exceptional cases and for limited periods that alcohol may be necessary to enable a patient to turn a critical corner. Its use is specially indicated in **exhausting fevers,** like typhoid, pneumonia and septic fevers. The beneficial effects are due not only because it acts as a food, but because it stimulates digestion of other foods, and in wasting and exhausting diseases it tends to prevent excessive tissue waste. Alcohol thus maintains the strength and nutrition of the patient, increases the output of the exhausted heart and makes it slower, regular and stronger. The tongue becomes moist, respiration less hurried, and in place of delirium the patient becomes quiet, free from excitement, and sleeps better so that strength is maintained. If alcohol fulfils these objects then it is doing good and its use should be maintained, if not it should be discontinued. The action should be carefully watched to get the stimulant effect and not the depressant one.

Prescribing hints.—It must be borne in mind while ordering alcoholic beverages, that the effects produced are modified by various circumstances, such as (*a*) the

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amount of volatile ethers they contain; this is of more importance than the actual alcoholic strength; (*b*) the degree of their dilution with water; (*c*) the age, toleration and habits as regards alcoholic drinks of the patient; (*d*) the amount of exercise taken by him; (*e*) the condition of his stomach, whether empty or full; (*f*) the condition of his excretory organs, especially the kidneys; and (*g*) the nature of the diseases for which they are given.

In many exhausting febrile or other diseases, patients can consume without intoxication a large amount of alcohol, even as much as one pint of brandy per diem. Sparkling wines (carbonic acid) facilitate absorption and produce a quicker action. Old brandy, whisky or port should be preferred as they contain less injurious ingredients. Children tolerate relatively larger quantities. In chronic diseases wines are more useful, but are liable to undergo fermentation in the stomach and are not so well borne by some patients. Red wines usually disagree when there is hyperacidity. Owing to the presence of malt and diastase, beer tends to produce obesity and aids digestion of carbohydrate foods.

Different varieties of wines should not be given at the same time, as they derange digestion. Small quantities in repeated doses with some easily digestible food are the best method of administration. Debilitated persons do well if an alcoholic drink is given an hour before food. Champagne, port, strong claret or beer may produce burning and aching of the rectum, and new and inferior brandy or whisky headache, because the latter contains fusel oil, furfural and many injurious aldehydes.

It should be avoided where there is gastric irritation and where the kidneys are diseased on account of its effect on the renal epithelium.

For continuous use $1\frac{1}{2}$ ozs. of pure alcohol is all that can be utilised as a food in the human body daily. Roughly, $1\frac{1}{2}$ ozs. of pure alcohol equals 3 ozs. of whisky or brandy, which is equal to $1\frac{1}{2}$ pegs, or is equivalent to 7 ozs. of sherry, 15 ozs. of champagne, claret or white wine.

2. General Anæsthetics and Narcotics

Narcosis is a "physiological condition in which the normal responsiveness or automatic activity of the living system—organism, tissue or cell—is temporarily decreased or abolished." Drugs which produce unconsciousness are called *narcotics*, and unconsciousness however produced is always accompanied by some degree of reflex inhibition. Consciousness is the function of the cerebral cortex, and the rapidity of the onset of narcosis varies, but the degree increases in a regular way with the amount given. In very small doses they produce a tendency to quietness, while in larger amounts

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they give rise to drowsiness, sleep, stupor, and finally loss of consciousness and coma. Narcotics therefore are used either to induce sleep or to produce surgical anæsthesia.

The narcotic effect of a drug persists as long as it remains in the blood in sufficient concentration, and no narcotic drug is known to get itself fixed in the brain cells so as to exert any late effects after the drug has been excreted from the general circulation. *Volatile narcotics* being rapidly absorbed and rapidly excreted by the lungs exert only a temporary effect; whereas the *non-volatile narcotics* are excreted *via* the kidneys only to a limited extent and therefore maintain their effect for a longer period. These are therefore largely used to maintain a state of sleepiness and mental dullness.

Many views have been advanced from time to time to explain the way these narcotics act, but still we are far from any definite knowledge as to their mode of action. Since the chemical structure of the different narcotics have very little in common between them to explain their common effect, attempts have been made to explain their action as the result of some physical effect on the function of the brain cells exercised from outside rather than a chemical union with any of its components. The chief narcotics are formed by the union of one or more hydrocarbon groups, *e.g.* ethyl or amyl, with polar groups, such as —OH, —CO, —NH—CO—NH_2. The hydrocarbon group is lipoid soluble, while the polar group is water soluble. In other words it is the physical property of a drug rather than its chemical affinities which determine the narcotic effect. Mayer and Overton have therefore advanced the theory of a close relationship between the narcotic action and their relative solubility in oil as compared to water, *i.e.*, a close parallelism between narcotic efficiency and partition coefficient, *i.e.*

$$\frac{\text{solubility in fat}}{\text{solubility in water}}$$

The higher this coefficient, the more powerful the narcotic action. It is assumed that these drugs exert their main action on the central nervous system by taking up the fats and lipoids which abound there. Lipoids are a chemically heterogeneous group of substances like lecithin, cholesterin, cerebrin, etc. Since every cell contains lipoid, a narcotic will pass into the constituents of these cells and so alter the physical condition of the brain lipoids and interfere with their normal activity as to produce an anæsthetic effect. This effect is regarded as the function of the narcotics, and depends on their solubility in fats and fat like substances. This theory however applies to narcotics of the aliphatic series, *viz.*, chloroform, ether, chloral hydrate, etc., while morphine and other basic and saline narcotics like bromides,

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do not obey this law; moreover, the peripheral nervous system though rich in lipoids is not affected by aliphatic narcotics.

Since it is known that deprivation of oxygen, as in asphyxia, causes anæsthesia or narcosis, and that narcosis is followed by diminished oxygenation, Verworn and his associates maintain that deficiency of oxygen produces anæsthesia. They argue that narcotics render the oxygen carriers of living tissues incapable of carrying oxygen. This view however is not generally accepted on the ground that diminished oxygenation may not be the cause of narcosis, but an effect of all narcosis which by suppressing irritability depress oxidation.

Traube has shown a close relationship between the narcotic power of a drug and its power to lower surface tension. Here is again a similar parallelism between the surface tension effect and the partition co-efficient, and it is not possible to say as to which property is the determining factor in narcosis. It is possible that both the factors participate to a varying extent in different tissues.

The real laws which govern the action of narcotics are not quite clear, and many carefully prepared substances have been found to possess totally different action from that anticipated. The reason why one drug acts as a narcotic than another is in many instances as obscure as is the cause which produces sleep or physiological narcosis.

The drugs of this group when used in sufficient concentration produce unconsciousness, muscular relaxation and abolition of all reflexes and pain so that operations can be performed without the patient feeling any pain. Most of these drugs belong to the aliphatic group, and being very volatile, some gaseous, they are rapidly absorbed by the lungs, therefore they are administered by inhalation. They should be quickly eliminated from the system so that the patient will regain consciousness as quickly as possible after the anæsthetic is discontinued, at the same time they must produce these effects without depressing the vital centres dangerously, or causing any permanent damage to the central nervous system. The study of general anæsthetics means a knowledge of their toxicology, the patient being drugged into a state of narcosis approaching collapse.

Within recent years certain non-volatile substances are being extensively used for the production of general anæsthesia and narcosis. These are used either by the mouth or as injection, the object being to produce partial narcosis, the anæsthesia being completed with some volatile or gaseous anæsthetic, or alternately with a spinal or local anæsthetic. They belong to two groups, viz.

(1) alkaloidal narcotics, viz. hyoscine and morphine;

(2) paraldehyde, avertin and derivatives of barbituric acid.

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These are used either for the production of general anæsthesia, or as basal narcotics preliminary to the use of volatile anæsthetics.

CHLOROFORMUM

Chloroform. $CHCl_3$

Source.—It is *trichloromethane* to which 1 to 2 p.c. v/v of dehydrated alcohol has been added. Prepared by the action of chlorine in the presence of alkali, on ethyl alcohol, industrial methylated spirit, or acetone.

Characters.—A colourless, volatile liquid; odour, characteristic; taste sweet and burning. *Soluble* in 200 parts of water, miscible with dehydrated alcohol, with ether, fixed and volatile oils, and with most organic solvents. Sp. gr. 1.485 to 1.490.

B.P. Dose.—1 to 5 ms. or 0.06 to 0.3 mil.

Official Preparations

1. **Aqua Chloroformi.**—0.25 p.c. **B.P. Dose.—½ to 1 oz. or 15 to 30 mils.**
2. **Spiritus Chloroformi.** *Syn.—Chloric Ether.*—5 p.c. **B.P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

Non-official Preparations

1. **Tinctura Chloroformi et Morphinæ Co.**—A substitute for chlorodyne. Contains chloroform ¾ m., morphine hydrochlor. $\frac{1}{11}$ gr., acid hydrocyanic dilute ½ m., in 10 ms. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.
2. **Chloroformum Camphoratum, B.P.C.**—Camphor 2, chloroform 1. Anodyne in *toothache.*
3. **Tr. Chloroformi Co., B.P.C.**—Chloroform 10, alcohol (90 p.c.) 40, tr. cardamomi co. 50. *Dose.*—15 to 60 ms. or 1 to 4 mils.

Pharmacology of Chloroform

Externally.—Chloroform when allowed to evaporate constricts the local blood vessels and paralyses the peripheral sensory nerves, and is a **local anæsthetic.** If the evaporation is prevented, or if it be rubbed into the skin, it causes redness and even vesication. It is an **irritant,** more powerful than ether, a general **protoplasmic poison,** and a powerful **antiseptic.**

Internally.—The same irritant action is observed in the mouth and stomach when chloroform is taken internally. In diluted solution it has a warm sweetish taste and acts as a pleasant **carminative** and **stomachic.** It produces a sensation of warmth in the epigastrium and increases the vascularity and secretion of the stomach. Vomiting often accompanies anæsthesia and is central.

Heart and circulation.—Chloroform is quickly absorbed by the lungs and in concentrations used in anæsthesia depresses the muscles of the vessels, the splanchnic vessels being more affected than those of the extremities. It also **depresses the vaso-motor centre.** As a result of dilatation of the vessels and the depressed condition of the

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heart the **blood pressure falls.** The skin becomes pale and cold, pulse soft, slow but regular, although there is quickening during the early stage from nervousness. Ordinarily the vaso-motor paralysis dominates and the heart beats efficiently even when the vaso-motor centre is paralysed.

The heart is very sensitive to chloroform, and experiments with isolated heart show that small amounts produce, after a momentary slowing, depression, rendering the beats smaller and ineffective. A concentration of 0.05 p.c. of chloroform in the perfused fluid will arrest the heart. It is therefore a **direct poison to the cardiac muscle.** In prolonged anæsthesia the heart is affected directly, supplemented by low blood-pressure and asphyxia. During anæsthesia the heart may stop suddenly through rapid absorption of concentrated vapour and reflex vagus stimulation. The cause of sudden failure of the heart has been the subject of much controversy. It may occur in the early stage of the anæsthesia, or when the inhalation is irregular, or even after the inhalation has been stopped. Since it does not occur if the vagi are cut or an injection of atropine is given, it has been suggested that the stoppage is due to inhibitory stimulation. Others, chiefly Levy, explain it as the result of fibrillation brought on by excessive irritability of the muscle from chloroform vapour. It is possibly due to excessive sympathetic stimulation acting on an already irritable heart, or to an increased secretion of adrenaline.

Respiration.—In the early stage the respiration is as a rule fairly regular, but deeper and quicker from stimulation of the centre; this is followed by depression of the respiratory centre. If the inhalation is given in large amounts the breathing becomes irregular from choking sensation and local irritation. During the stage of excitement it becomes more irregular, the patient holds his breath and then takes a few deep gasps allowing a large quantity of concentrated vapour into the blood. During the stage of anæsthesia the breathing becomes regular, though noisy, shallow and slow. If the administration is still prolonged it becomes stertorous and quick. The respiration may be temporarily stopped reflexly through irritation of the 5th nerve, *i.e.*, through nasal mucous membrane. Reflex closure of the larynx, accumulation of mucus and saliva may also interfere with respiration, and anæsthesia of the larynx may lead to suction pneumonia, which is more common with ether than with chloroform. Direct irritation, hæmorrhagic emboli or impurities in the anæsthetic used may also contribute to the formation of pneumonia.

Blood.—Both ether and chloroform when applied to drawn blood cause hæmolysis but this effect is observed in a minor degree in life. Owing to the diminution of plasma there is polycythæmia, but the hæmoglobin is reduced. In

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deep anæsthesia fibrinogen disappears from the blood thus diminishing its coagulability. This effect is possibly due to derangement of the liver and disappears with its repair.

Eye.—Its effect on the eye varies in different stages and depends upon the amount used. At first the pupil is dilated from stimulation of the sympathetic, though light reflex remains intact. Later there is contraction from stimulation of the oculo-motor centre and paralysis of the sympathetic. During profound anæsthesia the pupils dilate from paralysis of the centre and the reaction to light is also lost. This implies either (*a*) overdose, (*b*) asphyxia, or (*c*) reflex from operative procedure.

Kidneys.—During anæsthesia the secretion of urine is diminished. Albumin appears and in some cases fatty degeneration and permanent inflammatory lesions of the kidneys have been observed.

Therapeutics of Chloroform

Externally.—As a local anodyne, chloroform may be combined with liniments of aconite and belladonna (A. B. C. liniment) and applied in **myalgia, lumbago, chronic rheumatism,** etc. If counter-irritation is required the liniment may be sprinkled over a piece of cloth or lint and covered with oiled silk. A deep hypodermic injection (10 ms.) near the sciatic nerve relieves **sciatica.**

Internally.—A pellet of cotton wool soaked in chloroform and introduced into the cavity of a painful carious tooth relieves **toothache.** One or two drops may check **vomiting, sea-sickness** and **flatulent distension.** In diarrhœa or in the beginning of cholera spirit of chloroform may be usefully combined with opium or other astringents. Chlorodyne is a useful remedy in these cases. It is also useful in intestinal and other **colics.**

AETHER

Ether. Ethyl Oxide. $C_4H_{10}O$

Syn.—Ethylic Ether ; Sulphuric Ether.

Source.—Obtained by distilling a mixture of ethyl alcohol and sulphuric acid, rectifying the distillate.

Characters.—A colourless, transparent, very mobile liquid ; odour characteristic ; taste, sweet and burning. Very volatile and inflammable. Sp. gr. 0.720 to 0.724. *Soluble* in 8.5 volumes of water, miscible in all proportions with alcohol (90 p.c.), chloroform, fixed and volatile oils.

B.P. Dose.—15 to 60 ms. or 1 to 4 mils.

Official Preparations

1. **Æther Anæstheticus.** *Syn.—Æther Purificatus.*—Possesses the characters of ether. Sp. gr. 0.720.
2. **Spiritus Ætheris.**—Contains 33 p.c. ether. **B. P. Dose.—15 to 60 ms. or 1 to 4 mils. Enters into.**—Tr. Lobeliæ Ætherea.

Non-official Preparations

1. **Spiritus Ætheris Co.** *Syn.—Hoffmann's Anodyne.*—Ether 137·5

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mil., alcohol (90 p.c.) 1950·0 mil., sulphuric acid 900·0 mil., water 37·5 mil., sodium bicarb. *q.s.* *Dose.*—20 to 40 ms. or 1·3 to 2·6 mils.

2. **Injectio Camphoræ Ætherea, B.P.C.** *Syn.—Curschmann's Solution.*—Camphor 20 grm., ether 30 mil., olive oil to 100 mil. *Dose.*—4 to 15 ms. or 0.25 to 1 mil.

Pharmacology of Ether

Externally.—Being extremely volatile, ether cools the skin and even freezes the part so that if applied as a spray it produces **local anæsthesia.** The cooling is followed by burning. If evaporation is prevented, it acts as an irritant and even vesicant. It is a powerful **antiseptic.**

Internally.—It produces burning, a disagreeable and characteristic taste in the mouth and reflexly stimulates the secretion of saliva. In the stomach it is quickly absorbed, increases gastric secretion, expels gas and acts as a **gastric stimulant** and **carminative.** It is also a valuable **intestinal antispasmodic** and reflexly stimulates the heart.

Heart and circulation.—Whether administered by the mouth, hypodermically or as inhalation, ether stimulates the heart and there is a **rise of blood pressure.** These effects are reflex through stimulation of the accelerator and vaso-motor centres. The heart is also **directly stimulated.** In the early stage of the anæsthesia the pulse is quickened and the blood pressure is raised. During anæsthesia the cerebral and skin vessels are dilated but the intestinal vessels are constricted and the pressure remains unaltered. During the paralytic stage the vaso-motor centre is depressed, and the blood pressure falls slowly. The heart remains normal even after the stoppage of respiration.

Respiration.—At first the respiration becomes quicker and deeper through reflex stimulation from mouth, stomach and the respiratory passages. Large doses, as when given to produce anæsthesia, depress the respiratory centre, death being due to asphyxia from respiratory paralysis.

Uterus.—Moderate anæsthesia has little effect on the uterine contractions, although cases of death of the fœtus under ether or chloroform during labour are on record. This may be due either to a direct action on the fœtus or to asphyxia from low maternal blood pressure.

Kidneys.—During the anæsthetic stage the secretion of urine is diminished from constriction of the renal vessels, after this stage is over there is profuse diuresis. Albumin appears in the urine, which however soon passes off, though nephritis with albumin and even blood in the urine may appear in some cases.

Therapeutics of Ether

Externally.—For superficial minor operations, ether used as a spray produces sufficient anæsthesia for the purpose. As this effect does not extend into the deeper tissues, it is

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not suitable for deep surgical operations. It is used as an antiseptic for infected wounds.

Internally.—As a **carminative** and **antispasmodic**, ether is useful in some forms of dyspepsia, gastrodynia, and intestinal cramps. Hoffmann's anodyne is an excellent combination for the relief of **intestinal** and **biliary colic**, and in **hiccough** when used with ice.

Heart and lungs.—It is a valuable cardiac and respiratory stimulant when given by the mouth (10 to 40 ms.) or hypodermically (10 to 40 ms. dissolved in olive oil) in **syncope**, **fainting** and **cardiac failure** from any cause. Its effects are transient and it has to be repeated. It is also useful in **angina, spasmodic bronchitis,** and **whooping cough.** In the latter disease it is given intramuscularly in doses of 1 c.c. up to the age of 7 or 8 months, repeated daily or given on alternate days. But the pain and danger of necrosis are serious drawbacks to its use. It is given to tone up and allay the irritability of the heart in delirium tremens.

Ether and Chloroform as General Anæsthetics

Both ether and chloroform when inhaled produce general anæsthesia by their action on the central nervous system. This action may be conveniently described under *four stages* as follows :—

First Stage or that of **imperfect consciousness.**—This begins with a feeling of warmth on the surface, sounds in the head, flashes of light before the eyes, choking or suffocation, or sometimes cough (especially if the vapour is concentrated), and confusion of ideas. Sounds are faintly heard, questions are imperfectly answered, and pain, if present, is not much felt, indicating a blunting of the general sensibility.

Second Stage, or that of **general stimulation.**—The patient is no longer conscious of external impressions, but according to temperament, he may sing, cry, shout, or struggle (hence some authors call this "the struggling stage"). At times the struggling is so hard that the patient holds his breath, the face becomes livid, the eyes protrude and the jugular veins distend. Almost coincidently the **lower centres** are **stimulated**; the pulse becomes frequent, the heart and large vessels throb, respiration becomes quickened, blood-pressure rises and the pupils become slightly dilated through stimulation of the sympathetic.

Third Stage, or that of **anæsthesia.**—This is characterised by the *paralysis of the nerve-centres which have previously been excited, and the abolition of reflex action and sensation.* If the inhalation is continued, the patient becomes completely unconscious; his limbs quite flaccid, and if one of them is held up it falls like that of a corpse; only a sluggish contraction of the iris follows when the eyes are suddenly

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exposed to light; the **pupils** are **contracted** through stimulation of the oculomotor centre and paralysis of the sympathetic, and the **conjunctival reflex** is **completely abolished**. The pulse falls in volume and frequency, respiration becomes slow and deep, sometimes stertorous, and the blood-pressure falls from paralysis of the vaso-motor centre. This is the proper stage for operation. 1 to 4 drs. of chloroform is generally necessary to bring about complete anæsthesia.

Fourth Stage, or that of **paralysis** or **collapse**.—If chloroform is pushed further, the **lowest reflex centres** are **paralysed**, causing a **complete loss of muscular tone**, so that the patient passes urine and stools involuntarily, and the muscles become completely flaccid. Sometimes the surgeon is obliged to push the inhalation to this extent, to enable him to reduce dislocations or to examine abdominal viscera through the abdominal wall. If the inhalation is still continued, the **pupils dilate**, which is *an indication of the commencement of asphyxia* and of paralysis of the **vaso-motor, respiratory** and **cardiac centres**. It is therefore an important "*danger-signal.*" The blood-vessels and capillaries now dilate and the blood-pressure falls to zero. Respiration becomes shallower, weaker and irregular, and often stops before the arrest of the heart. The pulse grows feeble and intermittent, and finally the heart stops in diastole.

Causes of death under chloroform.—There has been much controversy as to whether death takes place from the heart or from the lungs. The two Commissions appointed by the Nizam of Hyderabad came to the conclusion that respiration fails before the heart. But the correctness of this view has been strongly disputed. There are three possible dangers in chloroform anæsthesia: *First*, occurring early before the patient is completely under, due to **heart failure**, caused by (*a*) *direct toxic action on the myocardium* of concentrated poison. The lung surface of absorption is extensive, hence a very concentrated dose passes into the pulmonary arteries; (*b*) *stimulation of the vagus centre*; this may be reflex from nose, larynx, trachea, or from pulmonary irritation by the concentrated vapour; or directly from high concentration which makes the centre hypersensitive; this is avoided by injection of atropine; (*c*) *increased peripheral resistance* from excessive reflex vaso-constriction; and (*d*) *fibrillation of the heart*, due to excessive irritability from chloroform vapour, or to increased output of adrenaline. *Second danger* is that owing to the depressing action of chloroform on the heart muscle there is a very **small margin of safety** between the stage of complete anæsthesia and that of complete paralysis or collapse and it is very difficult to resuscitate the patient. Whereas a concentration of 35 mg. to 100 c.c. of blood will produce anæsthesia, a concentration between 40 to 70 mgrm. per 100 c.c. is fatal. *Third*

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danger is the well known **delayed chloroform poisoning**, which may commence within a few hours to six days after the use of the anæsthetic. The symptoms are those of acute acidosis, there is persistent vomiting, fatty degeneration of the liver, heart and kidneys, leading to toxæmia, prostration, coma and death. This is more common in patients suffering from acetonuria, diabetes, cyclic vomiting, rickets and wasting diseases.

Dangers during administration.—Broadly speaking they may arise from two sources, *viz.* (1) failure of respiration, and (2) failure of the heart, as detailed below :—

1. Death from suffocation may be caused by :—

(*a*) *Obstruction of the glottis* by falling back of the tongue or the sucking in of vomited matter or blood.

(*b*) *Spasm of the glottis* from the inhalation of chloroform vapour, which is either too strong or contains irritating products of decomposition.

(*c*) *Mechanical impediments to respiration*, due either to (1) *constrained position of the patient* as in obstetric and renal operations ; (2) *pressure of tight clothes or bandages*, or the *assistant's arms* ; (3) *falling in of the lips and alæ nasi*, as in old people who have lost their teeth ; (4) *spasmodic holding of the breath* especially in nervous patients, and during the early stages of the administration.

(*d*) *Paralysis of respiration* occurs more often from ether than from chloroform, where deaths are due more from cardiac shock. If chloroform or ether is used freely diluted, the respiration stops before the heart, in more concentrated forms the heart continues to beat for a very short time. It is possible that the failure of respiration may be the effect of anæmia of the central nervous system from fall of blood pressure. Weakness of the heart therefore only indirectly affects respiration.

2. Death from the stoppage of the heart may occur from :—

(*a*) *Excessive concentration of chloroform vapour*, causing sudden paralysis of the cardiac muscle.

(*b*) *The shock of operation*, reflexly stopping the heart. This may happen even in trivial operations, especially if anæsthesia be incomplete.

(*c*) *Disease of the heart.* The heart is apt to fail if it is fatty, dilated, or structurally disorganised. Therefore it is risky to administer chloroform to the old, the infirm, the anæmic, drunkards, epileptics and those who suffer from valvular diseases. For them ether is the safest anæsthetic. A.C.E. mixture (alcohol 1, chloroform 2, ether 3) or the simultaneous inhalation of oxygen and chloroform vapour may also be resorted to in carefully selected cases.

(*d*) *Pressure on the carotid sinus.* Since external compression of the carotid sinus stimulates the adventitial sensory

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nerve-endings and reflexly slows the heart, or sometimes may cause complete arrest of the heart, it has been suggested that the nerve connections of the sinus and the effect of pressure on it may have some connection with the sudden stoppage of heart under an anæsthetic.

Kemp believes the cause to be a defect in function or substance of the adrenal cortex, with secondary dysfunction of the thyroid.

Recovery from anæsthesia.—The rapidity of recovery depends upon the amount of anæsthetic used and on the duration of administration. If after full anæsthesia the patient is just kept under with a few whiffs now and then recovery takes place very soon after the administration is stopped. The lowest functions reappear first, the respiration becomes quieter, the eye reflex and deglutition reflex appear next, then after a while consciousness returns. The mental equilibrium is established last. Coughing, retching and vomiting appear with return of consciousness.

Absorption and elimination.—Both ether and chloroform are absorbed and eliminated very quickly from the lungs, only a small part being excreted by the urine. At the beginning the amount excreted, *i.e.*, in the expired air is much less than in the inspired air, showing that there is retention of the anæsthetic in the body. They exist in the blood and tissues chiefly in physical solution, and are therefore absorbed and excreted by the alveolar blood in proportion to their concentration in the alveolar air. With ether light anæsthesia can be obtained at a concentration of 6 p.c. (by volume) of ether vapour, while deep anæsthesia requires 10.5 p.c. by volume. Fatal concentration with ether is 11 p.c. For chloroform the corresponding concentrations are 1.35 volume p.c. for light anæsthesia, and 1.65 p.c. for deep anæsthesia, and fatal concentration is 2 p.c. (Sollmann). The margin of safety between minimal anæsthetic and fatal dose therefore is greater with ether than with chloroform.

After effects of ether and chloroform.—(*a*) *Vomiting*, when slight is of no consequence, and is a sign of reaction from shock after operation. Sometimes it may be severe and may be due to (*i*) idiosyncrasy or digestive disturbances, (*ii*) a central effect, and (*iii*) excessive dose of chloroform. In the early stage vomiting is due to the taste and smell of the vapour.

(*b*) *Bronchitis and complication of the lungs.*—These occur chiefly from the use of ether which irritates the bronchi and in susceptible persons may set up bronchitis. It may even cause severe and fatal bronchial complications in persons suffering from pulmonary congestion, bronchitis and phthisis. Sometimes infection may occur from septic inhaler.

(*c*) *Acid intoxication.*—Administration of any lipoid-soluble anæsthetic reduces the alkali reserve of the blood,

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specially if the administration is prolonged. The danger is greater in conditions associated with acidosis, *e.g.*, in diabetes, eclampsia, vomiting of pregnancy, acute yellow atrophy of the liver, etc. In these conditions the use of glucose and bicarbonate of soda before starting the operation should be considered.

(*d*) *Renal irritation.*—In a certain percentage of cases, more with chloroform than with ether, albumin appears in the urine with casts. This usually disappears in persons with healthy kidneys, but in persons with diseased kidneys there may be fatal suppression of urine and occasionally fatty degeneration.

(*e*) *Troublesome flatulence and post-operative gastric and intestinal paralysis.*—These are more common with ether. The relaxation of the gastric muscles favours dilatation of the stomach and irregular peristalsis, which are responsible for the 'gas pains' so common with ether. Sometimes there may be spastic contraction of the colon with accumulation of gas and fluid above.

Cases unsuitable for chloroform.—Those suffering from anæmia, low blood-pressure, cachexia, angina, weak and fatty heart, Graves' disease, hæmorrhage and adenoids. Diabetics and any condition that favours acidosis, and those suffering from jaundice are also bad subjects for chloroform.

Cases unsuitable for ether.—Those suffering from laryngeal spasm or obstruction, and any disease of the lungs or pleura. Very old age, those suffering from atheroma, aortic aneurism and renal disease, and operations with cautery near the mouth are contra-indications for ether.

Accumulation of mucus or saliva often gives trouble by blocking the air way, and is more marked with ether. This is obviated by giving a preliminary injection of atropine, or by turning the head to one side to help drainage, or by swabbing out the mucus with mops. During the stage of muscular relaxation the falling back of the tongue obstructs the air passage.

Uses of general anæsthetics.—These are chiefly restricted to cases where surgical operations or manipulations are required and which will involve much pain and suffering to the patient. They are therefore used to annul pain and produce unconsciousness. Their field of usefulness has, however, within recent years become limited owing to our advance in knowledge regarding the different local anæsthetics, and the various improvements introduced with regard to their uses. In fact many operations which were formerly performed under general anæsthesia are now done with local anæsthetics with much success. There are however certain limitations to the use of local anæsthetics. Where complete relaxation of the muscles is essential to the success of the operation, or where any movement on the part of the patient may interfere with the success of the operation, or where we want to avoid any

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depressing effect associated with the operation in a nervous patient, chloroform and ether will continue to hold their field. Apart from their uses in surgical operations they may be used under the following conditions :—

1. *To produce anæsthesia of slight degree during labour* with moderate inhalation after full dilatation of the os. Deep anæsthesia is as a rule not required and only prolongs labour.

2. *To relax muscular spasm* during the reduction of dislocations or hernias, the setting up of fractures or during catheterisation.

3. *For the purpose of diagnosis*, as in the case of young children or hysterical subjects. For the examination of abdominal viscera or to ascertain whether a particular swelling is a real or a phantom tumour.

4. *To relieve the intense pain of certain diseases*, such as biliary, intestinal and renal colics, neuralgias, etc.

5. *To relieve the spasms* of many convulsive diseases, such as tetanus, strychnine poisoning, hydrophobia, puerperal eclampsia, chorea, uræmia, etc. The distressing dyspnœa of asthma and of cough and hiccough may be lessened by the inhalation of a few drops poured on a handkerchief.

Administration of chloroform.—The essential feature in the administration of chloroform is to avoid the danger of over concentration of the vapour, or of surcharging the blood by too rapid administration.

The following practical hints should be particularly attended to while administering chloroform :—

1. Chloroform should be perfectly pure. The A. C. (alcohol and chloroform) mixture or A.C.E. mixture is only indicated in cases where there is a fatty or weak heart, or where the operation is likely to be a protracted one.

2. All tight clothes about the neck, chest and abdomen should be removed or materially loosened. Attendant's or dresser's hands should not press upon the chest or abdomen while holding the patient.

3. Artificial teeth should be removed.

4. The safest position of the patient is the dorsal decubitus.

5. As the undivided attention of the chloroformist is essential for the safety of the patient, the operator should not undertake to administer the chloroform and to operate at the same time.

6. Chloroform should be freely diluted with air.

7. An ordinary handkerchief or a piece of lint folded in the form of an open cone within which some absorbent cotton has been stitched is the best inhaler in the absence of Junker's apparatus, which does not allow a greater concentration of chloroform than 5 per cent. If a cone is used it should not be held either too close to or too distant from, the mouth and the nose. The proper distance throughout the inhalation is the nearest which does not cause choking, struggling or holding of breath.

8. If the patient is weak, a small dose of brandy or whisky may with advantage be given before the inhalation is begun. A nervous patient should be brought into a calm state of mind as far as possible and an injection of morphine may be considered (*see* Basal Narcosis).

9. If lint is used, not more than 20 or 30 ms. should be sprinkled on to it at a time. Some anæsthetists prefer to commence with double this dose, so as to lessen the period of excitement.

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10. Pay particular attention to the breathing, as most of the accidents are caused by respiratory failure. Irregularity of breathing is generally caused by insufficiency of air, which makes the patient struggle, or hold his breath.

11. No operation should be commenced until the patient is under complete anæsthesia, as shown by the absence of the corneal reflex. The administration should never be pushed to the stage of stertorous breathing and complete relaxation of muscles, except when it is absolutely necessary as for the reduction of old-standing dislocations.

12. Directly the corneal sensibility is lost or respiration becomes stertorous, the inhalation must be suspended. In case the stertor comes on while the cornea is still sensitive, the inhalation should not be proceeded with, as it invariably happens that the cornea becomes insensitive within a few seconds afterwards.

13. The patient's head should invariably be turned to one side, the lower jaw depressed and the tongue drawn forward if necessary during vomiting, so that no vomited matter may enter the larynx. Should this accident happen laryngotomy must be at once performed.

14. Pallor of the face is best controlled by lowering the head and giving amyl nitrite inhalation.

15. Special care should be taken during an operation on the mouth to prevent any blood flowing down into the larynx. Full anæsthesia may be maintained by introducing chloroform vapour into the post-nasal space through a soft catheter connected with the Junker's inhaler; or by injecting morphine subcutaneously before the inhalation.

16. Lividity of the face and deep stertor should at once be controlled by raising the shoulders, opening the mouth, and pulling out the tongue. If breathing threatens to stop or stops altogether, artificial respiration should immediately be commenced and at the same time fingers may be thrust under the ribs to mechanically stimulate the heart. Artificial respiration should be maintained for at least an hour or so, and if there be any sign of returning life, it should be continued for several hours. In addition to the above measures, intra-cardial injection of adrenaline; strychnine, ether, and brandy hypodermically; the inhalation of carbon dioxide and oxygen, bandaging of the limbs, compression of the abdominal aorta and lowering of the head should all be tried.

Preparation of the patient.—During an emergency it is not possible to prepare the patient adequately, and it is surprising that as a rule no untoward result follows the use of an anæsthetic. Even under normal conditions the drastic methods of preparation followed before are avoided. The patient is given a preliminary purge, preferably castor oil, 36 hours before operation, and an enema on the evening before. Sometimes a rectal wash is given a few hours before the operation, but this weakens the patient and is not given except in cases of rectal operation. The patient should be kept on light food on the previous day, and no food is given on the morning of the operation to keep the stomach empty and avoid vomiting. A cup of tea and a slice of toast may however be given if necessary. Glucose or some form of sugar is of great service to replenish the carbohydrate reserve of the body and as a *preventive against post-anæsthetic vomiting and acidosis.* An injection of atropine is given as a routine method to prevent excessive perspiration, secretion of mucus and reflex vagus stimulation. It is more

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indicated when ether is used and should be given in full doses.

Treatment of untoward symptoms.—(a) *Cyanosis.*—When due to obstruction of the air way, as by excessive secretion, falling back of the tongue, etc., this should be rectified without delay. When due to respiratory weakness, it demands immediate withdrawal of the anæsthetic and administration of respiratory stimulants, e.g., atropine, coramine, or caffeine.

(b) *Weak and irregular pulse* should be treated by stoppage of further anæsthetic and administration of saline, either per rectum or intravenously, depending upon the urgency of the case.

(c) *Collapse.*—(i) In ether anæsthesia, whatever may be the stage of operation, it should be suspended and the patient put into Trendelenburg position. If from chloroform, keep the body level.

(ii) Lungs should be slowly and rhythmically inflated with CO_2 and oxygen (10 p.c. and 90 p.c.), or with pure oxygen.

(iii) Hot blanket to keep the body warm, and if neces sary, the limbs may be bandaged from fingers upwards.

(iv) Injection of atropine or caffeine in ether anæsthesia, and cardiac stimulants in chloroform collapse, *e.g.* camphor, coramine or cardiazol.

(v) Heart failure may be treated with intracardial injections of adrenaline, strychnine, camphor or glucose. But since all these drugs act in diverse ways, it has been suggested that the stimulation caused by the needle brings on recovery. Cardiac massage may also be tried.

Carbonic acid gas in anæsthesia.—This gas being the natural and efficient respiratory stimulant is of great use to the anæsthetist, and when used with oxygen it hastens the induction of anæsthesia by stimulating breathing. At the end of the anæsthesia it will help the elimination of the anæsthetic and thus lessen post anæsthetic complications. Besides preventing respiratory failure it counteracts shock. It is used in strength of 5 p. c. with oxygen.

Treatment after inhalation.—No food should be given for at least two hours after inhalation. Iced soups or jellies and iced milk with soda water may be given during the next 12 hours. Vomiting may be checked by the sucking of lumps of ice or by a teaspoonful of burnt brandy.

Method of administration of ether.—The routine method is by inhalation either by the open or closed method. The open method is safer but more anæsthetic is required and it takes a longer time to produce anæsthesia. Buxton recommends inhalation of ether with oxygen in cases where the introduction presents difficulties from spasms, cough, holding of breath, struggling with cyanosis, in alcoholics and in

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persons with weak vitality. Hewitt and Blumfeld advocate the administration of ether 3 parts and chloroform 2 parts by volume by the open method (Skinner's mask) to the exclusion of all other methods on account of its alleged safety and freedom from after effects. Recently ether is given per rectum dissolved in equal volume of olive oil, and may be combined with paraldehyde or chloretone. Ether 2 to 5 oz., olive oil 2 to 4 oz., and paraldehyde 2 to 4 drs. forms a suitable dose for an adult, depending upon the physique and depth of anæsthesia required. This is introduced by a siphon tube 20 minutes before the operation after emptying the rectum with a purgative followed by an enema. An hour before the operation a dose of morphine, or atropine and scopolamine is given. When the operation is over the unabsorbed portion is siphoned off and the bowel washed out with soap and water enema. This method spares the respiratory tract so that there is less salivary and bronchial secretion and there is less vomiting and nausea. It is specially indicated in operations about the mouth and throat. But the anæsthesia is not under full control, and may be followed by irritation and even hæmorrhage from the bowels. A few cases of death have been recorded in children possibly due to overdosage, or to absorption of an excessive quantity from unhealthy condition of the rectum.

Choice of anæsthetics.—There is a wide range of anæsthetics, both local and general, for the surgeon to make his selection from. The indications for both ether and chloroform have been fully discussed. It is only necessary to point out that in both cases the drug must be pure. If the anæsthesia requires to be prolonged, a combination of nitrous oxide, chloroform and ether, or alcohol, chloroform and ether may be selected. In cases where the heart is weak, or otherwise diseased, ether should be preferred, and chloroform avoided. But if damage to the heart is great, ether should also be avoided as being dangerous on account of the strain on the damaged heart during excitement. Children are specially susceptible to ether irritation, and it is not suitable for operations about the mouth and larynx. Sometimes a few whiffs of nitrous oxide gas makes ether more pleasant. Within recent years alkaloidal narcotics have been used with volatile anæsthetics, with the idea of producing complete anæsthesia without giving ether in high concentrations. With this idea hyoscine hydrobromide $\frac{1}{200}$ gr. or atropine sulphate and morphine hydrochloride is administered an hour before the anæsthetic is given. This combination reduces the concentration of ether necessary to produce anæsthesia and atropine will diminish the secretion of mucus so frequently seen with ether. Atropine is preferred to hyoscine as it does not depress the respiratory centre and also prevents reflex vagus inhibition of the heart.

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The differences between chloroform and ether are tabulated below :—

Ether	Chloroform
1. Ether is a weaker anæsthetic and should be used in a concentrated form : 6 p.c. by volume or 15 p.c. by weight.	Chloroform must be given well diluted ; 97 to 98 p.c. of air and 2 to 3 p.c. of chloroform.
2. Ether being inflammable, no fire should be brought close to the mouth.	Chloroform is not inflammable.
3. A large quantity (several ounces) is needed to produce anæsthesia.	A small quantity, 3 drs. to 1 oz., is enough.
4. The smell of ether is disagreeable.	The smell of chloroform is not disagreeable.
5. The stage of stimulation is very much protracted and there is more struggling.	The stage of stimulation is shorter, and therefore less struggling.
6. The stage of anæsthesia is shorter, and the degree of anæsthesia is less profound.	The stage of anæsthesia is more complete, and the degree more profound.
7. The fall of temperature is great (Hare observed 4.4°F. in man).	The fall of temperature is slight.
8. Nausea and vomiting common after-effects.	Nausea and vomiting less common after-effects.
9. Cardiac, respiratory, and vaso-motor centres are not readily paralysed ; hence ether is a *safer* anæsthetic.	Cardiac, respiratory and vaso-motor centres are readily paralysed, hence chloroform is *not* so safe an anæsthetic.
10. Bronchial and lung complications such as bronchitis, pneumonia are frequent.	Bronchial and lung complications are uncommon.
11. Elimination is slow, and the smell hangs about the body for a long period.	Elimination is rapid, and the smell does not hang about so long.
12. Death from syncope during inhalation is less probable in subjects of cardiac weakness.	Death from syncope is more probable in subjects of cardiac weakness.

Preliminary anæsthesia.—Recently attempts are being made to use some non-volatile narcotics as adjuvant drugs before the administration of the anæsthetic proper, with the object of protecting the nervous system by producing profound sleep, thus making the patient indifferent to subsequent happenings. In fact this method, which is known as **basal narcosis,** is receiving considerable importance, inasmuch as more reliance is being placed on these preliminary measures than on the subsequent anæsthetic. It obviates all nervous apprehensions and mental distress so often responsible for true shock. Moreover with the introduction of these preliminary anæsthetics the use of chloroform has been much curtailed, and the necessity of using large amounts of ether considerably reduced. The drugs used for the purpose are morphine, hyoscine hydrobromide, avertin, paraldehyde, amytal, nembutal, luminal,

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evipan and pernocton. These will be considered under their respective heads.

Anæsthetic Gases

AETHYLENUM

Ethylene. C_2H_4

Syn.—Olefiant Gas.

Source.—May be obtained from the products of decomposition of petroleum. Contains not less than 98 p.c. v/v of ethylene. It may be compressed in metal cylinders.

Characters.—A colourless, inflammable gas, with a slightly sweet odour and taste. One volume dissolves in 9.2 volumes of water, in about half a volume of alcohol (95 p.c.) at 25°C., and in about 0.05 volume of ether at 15.5°C.

Pharmacology and Therapeutics

At ordinary temperature and pressure ethylene exists as a gas and induces *general anæsthesia* when inhaled with oxygen. The effects are similar to those of ether which it resembles, but more rapid in onset, in which respect it resembles nitrous oxide gas. But being lipoid soluble its effects are stronger than nitrous oxide, and the anæsthesia is sufficiently deep to be employed for operations requiring muscular relaxation.

The gas as obtained in compressed cylinders has a garlic smell and although the patient does not perceive it for more than a few breaths, it is annoying to the anæsthetist and other occupants of the room.

The usual practice is to give 90 p.c. of the gas with 10 p.c. of oxygen. For prolonged use it should be more freely diluted with 20 p.c. oxygen. As a rule the period of excitement is absent or relatively slight and the **respiration is not affected,** but remains slow and regular. The medullary centres are stimulated slightly by the lowered oxygen concentration. The skin remains dry and there is no perceptible increase either of perspiration or of salivary secretion. Post-anæsthetic vomiting and gas pain are rare, and less common than with ether.

Recovery takes place quickly, within two to three minutes, after withdrawal of the anæsthetic.

It is used in the same way and with the same apparatus as nitrous oxide: it is however safer, being free from asphyxia or cyanosis. As compared to nitrous oxide gas it produces complete muscular relaxation and deeper anæsthesia. Moreover excitement is less and recovery is more quick.

It differs from ether in being more pleasant, prompt and safe. There is absence of gas pain and vomiting, renal and pulmonary complications.

Caution.—The gas is inflammable and when mixed in

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certain proportions with air or oxygen it becomes explosive. It should not be used where open flame or cautery is used.

NITROGENII MONOXIDUM

Nitrous Oxide. N_2O

Syn.—Laughing Gas.

Source.—Prepared by heating ammonium nitrate. Supplied compressed in metal cylinders. Contains not less than 93 v/v of nitrous oxide.

Characters.—A colourless gas, heavier than air, with a characteristic odour and faint sweetish taste.

Pharmacology and Therapeutics

Nitrous oxide is a gas and produces **general anæsthesia** almost instantaneously, partly by direct narcotic action on the central nervous system and partly by exclusion of oxygen. The mixture used contains 20 p.c. of air and so 4 p.c. of oxygen, therefore the inhalation cannot be continued for more than a few minutes. Nevertheless it produces sufficient anæsthesia to enable the surgeon to perform small operations, like extraction of tooth or incision of an abscess, painlessly.

The anæsthesia is brought about so quickly that the different stages can hardly be differentiated. At the beginning there is some buzzing of the ear and indistinctness of vision, soon followed by impairment of consciousness, a pleasurable sensation, and a tendency to laugh (hence the name laughing gas). As soon as the inhalation is stopped the patient returns to consciousness, and the cyanosis disappears within half to quarter of a minute. The pulse becomes slower and fuller, and the respiration returns to normal.

For prolonged anæsthesia the gas is used with oxygen, or given after a preliminary dose of morphine and hyoscine, as then the anæsthesia can be produced without the risk of asphyxia. When given with oxygen there is less disturbance of the vital centres than with any other general anæsthetic. Moreover the anæsthesia can be prolonged without any fall of blood-pressure, depression of respiration or post-operative shock.

It is impossible to obtain with nitrous oxide and oxygen alone sufficient muscular relaxation, because at the ordinary atmospheric pressure the blood cannot take up sufficient nitrous oxide to produce deep anæsthesia. If, however, it is used with small quantities of ether, a relaxation of the muscle is obtained which is out of proportion to the amount of ether used, and this becomes more marked when ether and chloroform are used in combination. To secure better control of the proportion of gas and oxygen various forms

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of apparatus have been devised. For small operations it is administered through a tight-fitting mask to exclude air.

As a rule no after-effects are observed, and it is practically devoid of any danger except asphyxia from want of oxygen which may cause a rise of blood pressure to a dangerous extent in elderly persons. Some complain of giddiness, headache and drowsiness.

Contra-indications.—Elderly persons with arterio-sclerosis, those suffering from valvular and myocardial disease, obese and anæmic persons, and in operations on the brain.

AETHYLIS CHLORIDUM

Ethyl Chloride. C_2H_5Cl

Syn.—Kelene.

Source.—Obtained by the action of hydrogen chloride on ethyl alcohol, or on Industrial Methylated Spirit.

Characters.—Gaseous at normal temperatures and pressures, but as usually supplied is condensed into colourless, mobile, inflammable, and very volatile liquid. *Odour* pleasant and ethereal. Slightly soluble in water, miscible with alcohol (90 p.c.), and ether.

Pharmacology and Therapeutics

Elthyl chloride is both a local and general anæsthetic, and being extremely volatile is largely used in the form of spray to produce local anæsthesia in **dental practice** and **minor surgery**. As this anæsthesia does not penetrate into the deeper tissue it cannot be used for deep surgical operations. When inhaled it resembles chloroform in its action and depresses the heart like chloroform, though less powerfully. Consequently the blood-pressure falls, due partly to the depressed action of the heart and to the relaxation of the blood-vessels. Being very volatile it is administered in a concentrated form, for this purpose a mask similar to that used for nitrous oxide gas may be used. An ordinary glass funnel with some loose absorbent cotton-wool serves the purpose equally well; the broad end being placed over the mouth, ethyl chloride is sprayed upon the cotton through the small end. It should be remembered that excepting in children, corneal reflex is not lost in ethyl chloride anæsthesia, and that it is not of much value when muscular relaxation is required. Ethyl chloride is a comparatively safe anæsthetic and may be used to produce primary anæsthesia before administration of ether or chloroform. It is contra-indicated in serious diseases of the heart and myocardial degeneration, where ether is safer.

[3. Hypnotics

Hypnotics are drugs or measures employed to induce or maintain sleep. Sleep is a natural phenomenon which comes on spontaneously when the reflex activity of the central nervous

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system is inhibited to a degree which is usually accompanied by unconsciousness. The unconsciousness is not deep, as in coma, but more or less shallow. Like most habits, sleep is to a certain extent under voluntary control and is a natural sequence which follows after a period of wakefulness. Prolonged sleeplessness is accompanied by various pathological changes in the cerebral cortex and the appearance of some toxin in the blood.

A proper use of hypnotics implies a knowledge of the mechanism of sleep and the different factors concerned in producing sleeplessness or insomnia. As long as the mechanism of sleep remains in part unexplained the treatment of insomnia must at best be empirical. Whatever may be the underlying factors in the production of natural sleep, it is evident that in the majority of cases of insomnia the cause is the presence of some factors inimical to that state of physical or mental equanimity so essential to natural sleep, and the rational course of treatment would be to remove the disturbing factor.

The following factors are mostly responsible for sleeplessness :—

I. **Obstructive.**—1. *Pain*, from whatever cause it may arise, and the proper treatment is to allay the pain either by dealing directly with the primary disease responsible for it, or to make the patient forget its presence by the use of such drugs as morphine or any of its allies, barbiturates or other analgesics according to the intensity of the case.

2. *Certain general and visceral diseases.*—Diseases of the heart, vessels, kidneys, etc., often cause sleeplessness. Cough and dyspnœa are often responsible for sleeplessness. Cough may be a part of serious lung complication, or due to some local trouble in the throat. The rational treatment is to remove the disturbing factor, whenever possible, supplemented by the use of proper hypnotic drugs. Digitalis will often induce sleep in dyspnœa from failure of the heart.

3. *Intoxications.*—Excessive tea and coffee drinking often cause insomnia. With some people a cup of tea or coffee before bedtime will cause sleeplessness.

4. *Infectious Diseases*, when accompanied by high fever, *e.g.* malaria, pneumonia, etc.

5. *Diseases of the Brain.*—(*a*) organic, as tumour, meningitis, syphilis; and (*b*) mental, as mania, delirium tremens, etc.

II. **Psychoneurosis.**—By far the largest number of insomnia comes under this head which plays an important part in the mental and emotional excitement. These may be worry, grief, neurasthenia, hysteria, hypochondria, etc. A state of anxiety of preoccupation is a common factor in the production of insomnia, for instance the dread of not being able to sleep, active mental work, exciting companions, disturbing

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surroundings, etc., before sleep. Oftentimes the patient goes to bed with his mind fixed on the necessity of sleep—a state specially liable to perpetuate sleeplessness.

According to Verworn sleep is due to (1) lessened irritability, *i.e.*, fatigue of the cells of the cerebral cortex which results from work; (2) removal of external stimuli, as noise, light, etc. A sound which is of a monotonous nature, *e.g.*, continuous falling of rain, or a mild form of peripheral stimulus, which will not excite any emotion, will have a soothing effect on the brain cells conducive to sleep. Many cases of insomnia due to psychoneurosis yield to suggestion. If the patient knows that he will get something for sleep, the knowledge will of itself bring on sleep. At the same time if he knows that the drug is to be discontinued or the dose reduced, the dread of a sleepless night will cause insomnia. Similarly if an injection of, say morphine is given to produce sleep, oftentimes an injection of some inert substance, even water, will have the same mental effect to produce sleep. The effect of monotonous sound, monotonous thought and monotonous sight in the production of sleep is well depicted by Wordsworth.*

The different hypnotics vary in their speed of action, duration of their effect and suitability for various ages and physical states. It is useless for instance to order a hypnotic when the patient is up and about, or to prescribe paraldehyde to a patient who goes to sleep in time but wakes up after 3 to 4 hours.

The action of hypnotics resembles somewhat that of general anæsthetics, but is slower in its onset, less powerful, more lasting, and is not intended to produce a deep stage of narcosis. An ideal hypnotic must not irritate the stomach and should be absorbed readily, so that sleep may be induced at a regular interval after its administration and without producing any preliminary excitement. It should not be volatile and must not be excreted too rapidly by the lungs. It should not produce any narcotic effect, *i.e.*, should not depress the cerebrum more than the sleep stage, and should have no untoward effect either on the vital medullary centres, or the heart. Moreover it should not have any toxic effect even when used for a prolonged period and should not form a habit. Such an ideal hypnotic is not known at present.

Of the different hypnotics, chloral, bromides, paraldehyde, avertin act by depressing the cerebral cortex; while the

* "A flock of sheep that leisurely pass by,
One after one; the sound of rain, and bees
Murmuring; the fall of rivers, wind and
seas,
Smooth fields, white sheets of water, and
pure sky;
I have thought of all by turns, and yet do lie
Sleepless!"

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barbituric acid group act by depressing the thalamic region. The barbiturates therefore, in addition to the hypnotic effect, are markedly sedative and are of great service in conditions characterised by motor hyperexcitability. Morphine and hyoscine are supposed to act on both the regions.

(*a*) Opium and Morphine Group

These relieve pain and also act as narcotics when used in large doses.

OPIUM

Opium. N.O. *Papaveraceæ*

Syn. I.V.—*Afim*, Beng., Hind. *Ahifen*, Sans.

Habitat.—Asia Minor, China, Persia, and India (Bihar and Malwa).

Source.—Obtained by incision from the unripe capsules of *Papaver somniferum*, and inspissated by spontaneous evaporation. It contains in its moist condition, not less than 9.5 p.c. of morphine.

Characters.—More or less rounded, usually somewhat flattened masses, varying in weight, from 250 and 1000 grammes; covered with portions of poppy leaves, and usually with fruits of species of *Rumex* adhering to the masses. When fresh, plastic, becomes hard and tough on keeping, or brittle. Odour, strong and characteristic. Taste, bitter.

Varieties.—(*a*) *Turkey opium*, produced in Asia Minor, in rounded, irregular, or flattened masses, usually enveloped in poppy leaves or fruits of a species of *Rumex* to prevent the masses from adhering to one another. Two varieties, viz. "Soft Shipping," which may contain up to 30 p.c. of moisture, and the "Druggists opium" which contains less moisture and less per cent. morphine. (*b*) *European opium*, chiefly produced in Belgium, Greece and Yugoslavia, is of a higher quality than the "Soft Shipping" variety of Turkey opium which it resembles in general characters. (*c*) *Persian opium*, in brick-shaped masses weighing about 1 lb. usually wrapped in red paper tied with red or yellow string; it contains less moisture, is homogeneous in character, and usually contains varying proportions of native gum, to give the consistence suitable for moulding them into bricks. (*d*) *Indian opium*, occurs in two forms, viz. *Abkari* or *excise opium* in square cakes covered with Nepal paper; *Medicinal opium*, in cakes and powder.

Composition.—The chemistry of opium is complex. It consists of:

(1) *Primary alkaloids*, 18 in number which form a closely related series at one end of which stands *morphine*, with its dominant property, the narcotic one, and at the other end *thebaine* with a typical strychnine action on the cord. On account of these other substances opium is less narcotic than morphine:—

Morphine up to about 5 to 21 p.c.	Pseudo-morphine	Meconidine
Codeine about 0.3 to 4 p.c.	Cryptopine	Rhœadine
Thebaine about 0.3 p.c.	Protopine	Codamine
Anarcotine or *Narcotine*, 2 to 7 p.c.	Hydrocotarnine	Gnoscopine
Narceine	Laudanine	Lanthopine
Papaverine	Laudanosine	Xanthaline

The important alkaloids belong to two groups, (1) *Phenanthrene alkaloids*, viz. morphine, codeine and thebaine; and (2) *Isoquinoline alkaloids*, viz. narcotine, papaverine, laudanosine, narceine, hydrocotarnine, etc.

(2) *Secondary Alkaloids or Derivatives*, 8 in number:—

Apomorphine	Apocodeine	Thebenine	Cotarnine
Oxydimorphine	Desoxycodeine	Porphyroxine	Rhœadenine

(3) *Indifferent Substances*, 3 in number:—

Opionin Meconin Meconoidin

(4) *Organic Acids*, 2 in number:—Lactic acid Meconic acid

(5) *Water.*—About 16 p.c.

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(6) Resin, glucose, fats, caoutchouc, essential oil, odorous substances and salts of ammonium, calcium, and magnesium.

Variation in composition.—The percentage of morphine varies in Patna opium from 3 to 5, and in Smyrna opium from 5 to 10½, whereas that of narcotine in the former 4 to 6 and in the latter 1 to 2.

Incompatibles.—Tannic acid and astringent vegetable preparations, salts of zinc, copper, iron, arsenic, lead and silver. Alkalies, their carbonates, and ammonia.

OPIUM PULVERATUM

Powdered Opium

Syn.—Pulvis Opii.

Source.—Opium dried at a moderate temperature, reduced to a fine or moderately fine powder, and adjusted if necessary, by the addition of powdered lactose to contain 10 p.c. of morphine, or $\frac{3}{10}$ gr. morphine in 3 grs.

Characters.—A light brown powder, consisting of yellowish-brown or brownish-red particles; odour and taste, of opium.

B.P. Dose.—½ to 3 grs. or 0.03 to 0.2 grm.

Official Preparations

1. **Extractum Opii Siccum.**—Contains 20 p.c. of morphine, or $\frac{1}{5}$ gr. in 1 gr. **B.P. Dose.**—¼ to 1 gr. or 0·015 to 0.06 grm.
2. **Pulvis Cretæ Aromaticus cum Opio.**—Contains 2.5 p.c. of opium, or 0.25 p.c. of morphine; or $\frac{1}{7}$ gr. morphine in 60 grs. **B.P. Dose.**—10 to 60 grs. or 0.6 to 4 grm.
3. **Pulvis Ipecacuanhæ et Opii.** *Syn.*—*Pulv. Ipecacuanhæ Co.*; *Dover's Powder.*—10 p.c. of opium, or 1 p.c. morphine; or $\frac{1}{10}$ gr. morphine in 10 grs. **B.P. Dose.**—5 to 10 grs. or 0.3 to 0.6 grm.
4. **Suppositorium Plumbi cum Opio.**—Lead acetate 3 grs. and powdered opium 1 gr. in each.
5. **Tinctura Opii.** *Syn.*—*Laudanum.*—Contains 1 p.c. morphine, or ½ gr. in 30 ms. **B.P. Dose.**—5 to 30 ms. or 0.3 to 2 mils.
6. **Tinctura Opii Camphorata.** *Syn.*—*Tr. Camphoræ Co.*; *Paregoric*; *Paregoric Elixir.*—0.05 p.c. w/v morphine, or $\frac{1}{37}$ gr. in 60 ms. **B.P. Dose.**—30 to 60 ms. or 2 to 4 mils.

Non-official Preparations

1. **Pilula Plumbi cum Opio, B.P.C.**—Lead acetate 1⅜ grs. and opium about ¼ gr. for each pill with syrup of glucose. *Dose.*—1 to 2 pills.
2. **Pulvis Kino Co.**—Kino 75, opium 5, cinnamon 20. 5 p.c. opium. *Dose.*—5 to 20 grs. or 0.3 to 1.2 grm.
3. **Unguentum Gallæ cum Opio.**—Ointment of gall and opium. Opium 7½ p.c.
4. **Nepenthe.** *Syn.*—*Anodyne Tincture.*—Similar to, and is given in same dose as, Tinctura Opii. Contains 0.84 p.c. morphine.
5. **Liquor Opii Sedativus, B.P.C.**—Opium, 100; calcium hydroxide, 15; alcohol (90 p.c.), 200; sherry-type wine, 150; hydrochloric acid, 15.6; water q.s.; alcohol, (60 p.c.) q.s. Contains 0.95 to 1.05 p.c. w/v morphine. *Dose.*—5 to 30 ms. or 0.3 to 2 mil.
6. **Pilulæ Hydrargyri c. Creta et Opii.** *Syn.*—*Hutchinson's Pills.*—Grey powder and Dover's powder, each 1 gr.; compound acacia powder $\frac{1}{2}$ gr., syrup of glucose q.s. for each pill. *Dose.*—One pill.
7. **Narcotina.** *Syn.*—*Anarcotine.*—White inodorous crystalline prisms. Insoluble in water. It is not a hypnotic but is an antiperiodic, in which respect it resembles quinine. *Dose.*—1 to 3 grs. or 0.06 to 0.2 grm.
8. **Cotarnine Chloride, U.S.P.** *Syn.*—*Stypticin.*—The chloride of an alkaloid prepared from narcotine. Occurs in yellow crystalline

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powder; very soluble in water and alcohol. Is allied to hydrastine. Useful in *uterine hæmorrhage*, and to check bleeding from the urethra after catheterisation. *Dose, U.S.P.*—0.06 gm. or 1 gr.

9. **Papaveretum.** *Syn.—Omnopon; Pantopon.*—Consists of the hydrochlorides of alkaloids of opium. Contains 4.75 to 52.5 p.c. morphine. Soluble brown powder. Used for the same purposes as opium. Usually used hypodermically. A 2 p.c. solution in a mixture of 3 parts of water and 1 part of glycerin is suitable for internal administration or hypodermic use. The preparations for injection may be sterilised by heating. *Dose.*—0.01 to 0.02 grm. or $\frac{1}{6}$ to $\frac{1}{3}$ gr. by mouth; 0.005 to 0.01 grm. or $\frac{1}{12}$ to $\frac{1}{6}$ gr. by injection.

MORPHINAE HYDROCHLORIDUM

Morphine Hydrochloride. $C_{17}H_{19}NO_3,HCl,3H_2O$

Source.—Hydrochloride of an alkaloid, morphine, obtained from opium.

Characters.—Colourless, glistening needles or crystalline powder; odourless; taste, bitter. *Soluble* in 25 parts of water, 50 parts of alcohol (90 p.c.), insoluble in ether and chloroform. Aqueous solution neutral to litmus.

B.P. Dose.—$\frac{1}{8}$ to $\frac{1}{3}$ gr. or 0.008 to 0.02 grm.

Official Preparations

1. **Liquor Morphinæ Hydrochloridi.**—Contains 1 p.c. w/v of morphine hydrochloride, or $\frac{1}{4}$ gr. in 30 ms. **B.P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

2. **Suppositorium Morphinæ.**—Contains $\frac{1}{4}$ gr. in each.

3. **Trochiscus Morphinæ et Ipecacuanhæ.**—$\frac{1}{32}$ gr. morphine and $\frac{1}{10}$ gr. ipecacuanha in each.

Non-official Preparations

1. **Linctus Morphinæ, U.C.H.**—Liq. Morph. Hyd. 3 ms., Chloroform emulsion 3 ms., Glycerin or Treacle 60 grs., Water to 1 dr. *Dose.*—1 dr. 3 or 4 times or oftener daily. Children of 8 to 14 years, 10 to 20 drops.

2. **Tinctura Chloroformi et Morphinæ Composita.**—Chloroform $\frac{3}{4}$ m., Acid. Hydrocyanicum Dil. $\frac{1}{4}$ m., and Morphine Hydrochlor. $\frac{1}{11}$ gr. in 10 ms. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.

MORPHINAE TARTRAS

Morphine Tartrate. $(C_{17}H_{19}NO_3)_2,C_4H_6O_6,3H_2O$

Source.—A tartrate of an alkaloid, morphine, obtained from opium.

Characters.—Minute, acicular, colourless crystals; odourless; taste, bitter. Effloresces on exposure to air. *Soluble* in 11 parts of water, sparingly in alcohol (90 p.c.), almost insoluble in ether and chloroform. Aqueous solution neutral to litmus.

B.P. Dose.—$\frac{1}{8}$ to $\frac{1}{3}$ gr. or 0.008 to 0.02 grm.

MORPHINAE ACETAS

Morphine Acetate. (Not official)

Source.—The carefully dried salts obtained by neutralising morphine with acetic acid. A white crystalline or amorphous powder. *Solubility.*—1 in $2\frac{1}{2}$ (almost) of water, 1 in 100 of alcohol (90 p.c.), 1 in 5 of glycerin.

Dose.—$\frac{1}{8}$ to $\frac{1}{3}$ gr. or 0.008 to 0.02 grm.

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Additional Non-official Preparations

1. **Morphina.**—The chief alkaloid of opium. A white crystalline powder. *Solubility.*—1 in 1000 of cold water, 1 in 100 of alcohol, 1 in 10 of oleic acid. *Dose.*—0.008 gm. or $\frac{1}{8}$ gr.

2. **Dionin.** *Syn—Ethyl-Morphine Hydrochloride, U.S.P.*—A white or yellowish crystalline powder, soluble in water. Pleasant substitute for morphine without its undesirable effects. Recommended in morphine habit. It has properties intermediate between morphine and codeine, but does not depress respiration to the same extent as morphine. Relieves dry *hacking cough.* Useful in *bronchitis* and *whooping cough.* A useful anodyne in *glaucoma, iritis, corneal ulcers,* etc., when used locally. *Dose, U.S.P.*—0.016 gm. or $\frac{1}{4}$ gr.

3. **Morphinæ Sulphas, U.S.P.**—Colourless acicular crystals. *Solubility.*—1 gm. in 15.5 c.c. of water, freely in hot water. *Dose, U.S.P.*—0.008 gm. or $\frac{1}{8}$ gr.

4. **Papaverine Sulphate.**—A white crystalline soluble salt. *Antispasmodic* in intestinal, biliary and renal colics and bronchial asthma. Useful in *vomiting* of pregnancy and after anæsthesia. It has no action on the heart. In *angina pectoris. Dose.*—2 to 4 grs. by mouth or hypodermically.

5. **Dilaudide.**—*Hydrochloride of dihydromorphine.* Colourless, bitter crystals, freely soluble in alcohol and water. Resembles morphine in action as analgesic. Affects respiratory centre like morphine. Used as a substitute of morphine, does not cause severe constipation and is less liable to form habit. *Dose.*—0.0012 to 0.0025 grm. or $\frac{1}{50}$ to $\frac{1}{25}$ gr. by mouth; 0·002 grm. or $\frac{1}{33}$ gr. subcutaneously.

6. **Eukodal.**—Hydrochloride of dihydroxycodeinone. Prepared from thebaine. A substitute for morphine as an analgesic and sedative. Depresses the vagal centre. Used in all cases where morphine is indicated. Does not produce vomiting or constipation. Though prepared from non-habit forming drug it is liable to produce a habit. *Dose.*—As analgesic, 0.005 to 0.01 grm. or 1 to 2 tablets.

Pharmacology of Opium and Morphine

Externally.—Opium and its alkaloids have no action on the sensory nerve endings or on the peripheral nerves. As morphine is absorbed to a slight extent from the unbroken skin and freely from the mucous membrane there may be some central analgesia.

Internally. **Mouth and stomach.**—In moderate doses opium causes dryness of the mouth, tongue and throat from **diminished secretion** due to its depressant action on the secretory centre of the salivary and the mucus glands. In the stomach small doses ($\frac{1}{12}$ gr.) **diminish the sensation of hunger** and slightly increase its movements; but larger doses cause **contraction** of the **pyloric sphincter** and relaxation of the fundus, and retards the passage of its contents by several hours. The gastric movements are diminished and the secretion is reduced, though it is subsequently increased. Opium therefore relieves pain, lessens appetite and retards digestion. These effects are central and observed after the drug is absorbed. It often causes nausea and vomiting which are not due to irritation of the gastric nerves, since they are not so marked in the early stage, but occurs during recovery from its effects and

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even when used subcutaneously. It is possibly due to the formation of some compound with an apomorphine effect on the centre. The centre is subsequently depressed, and in poisoning afferent impressions or direct emetics do not induce vomiting.

Intestine.—In the intestine opium **produces constipation, reduces secretion** and **relieves pain.** The cause of constipation has been the subject of much controversy and has been differently explained by different observers. While some demonstrated diminished peristalsis, others claimed marked stimulation. Apart from individual variations, it is possible that the presence of other alkaloids, specially papaverine and narcotine, which have a strong depressant action on peristalsis, may be responsible for the difference in the effects produced. All recent observations however tend to indicate that with morphine the peristaltic activity is diminished or unchanged in the jejunum and increased in the ileum and large intestine, which in the case of the latter may take the form of spastic contraction. These effects suppress the normal peristaltic waves and retard the passage of the contents downwards. The spasm of the ileo-cæcal and anal sphincters together with the tonic contraction of the pyloric sphincter, already referred to, allow the food materials to remain for a longer time thus helping more complete absorption of fluids and accumulation of inspissated fæcal mass. Moreover owing to the central effect, the rectal sensation is diminished and the defæcation reflex becomes sluggish. Opium therefore is a **sedative, astringent** and **anodyne** to the bowels. It also relieves, through central effect, pain and irregular peristalsis thus relieving colic. In intestinal colic, therefore, opium by relieving spasm may cause evacuation of the bowels. The secretion of pancreas is diminished by its direct action on the gland.

To sum up the different factors concerned in producing constipation :—(1) delay in emptying the stomach owing to pyloric spasm and relaxation of the stomach wall ; (2) diminished reflex peristalsis owing to loss of sensation ; (3) spasm of ileo-cæcal and anal sphincters ; (4) spastic contraction of the colon ; and (5) sluggish rectal sensation and defæcation reflex.

If a large dose is introduced directly into the circulation of animals like cat or dog, it causes vomiting and purging through increased tonus and peristalsis of the muscles of the intestine. No such effect is however observed in man even in poisoning or when a large dose of morphine is given as injection, except vomiting. It has been suggested that the action of morphine depends on two factors, one when the drug is in the blood and the other when excreted into the gut. Augmented peristalsis occurs during the time the drug is in circulation and is due to a depressant effect on the

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sympathetic ganglia, splanchnic being the inhibitory nerve to the intestine. When the drug is excreted into the intestine the effect is opposite to augmented peristalsis and it is for this effect that opium is extensively used and is due to some effect on the peripheral nervous mechanism. It should be noted that opium is superior to morphine in relieving intestinal pain and producing constipation, due firstly to its slow absorption, and secondly to the presence of isoquinoline derivatives, *viz.*, papaverine and narcotine which induce immediate relaxation of the plain muscles.

Liver.—Biliary secretion is considerably reduced, causing the stools to be pale or clay-coloured, or jaundice may set in. The amount of sugar in diabetic urine, and that of urea and carbonic acid, according to some authorities, are diminished.

Blood and circulation.—Morphine is rapidly absorbed from all mucous surfaces and soon disappears from the blood being partly fixed in the organs but largely destroyed, so that only a small fraction can be recovered in the autopsy. In moderate doses it has very little effect on the heart, except that it is **slowed from stimulation of the vagal centre**, and **slightly strengthened** in force. This effect is antagonised by atropine. The cardiac muscles are only indirectly affected in large doses through low blood-pressure and asphyxia. But the circulation remains fairly good till the last; in fact death in opium poisoning is *not due to the failure of the heart, but to the paralysis of the respiratory centre*, as will be seen presently. The blood-pressure is not influenced in therapeutic doses, and excepting the flushing of the face no change is noticed in the peripheral vessels. During asphyxia the face becomes cyanotic and of purple colour due to the vessels remaining dilated. As asphyxia advances the pulse may become slow, while the blood-pressure varies depending upon the vaso-motor centre and the heart. Since these effects can be abolished by aerating the blood sufficiently by artificial respiration these effects are indirect through the respiratory centre.

Respiration.—In small non-narcotic doses morphine will quiet the respiration, making it slow specially if it was quick, and increase its depth if it was shallow. In larger doses it causes **depression of respiration** and in cases of poisoning the respiration becomes very slow, even down to three or four per minute. The individual respirations eventually become shallow and irregular and before death assumes **Cheyne-Stokes** type. During natural sleep and also in sleep following a hypnotic the breathing becomes slow because less oxygen is required for the inactive body, but the CO_2 content of the blood remains unchanged. In morphine poisoning the CO_2 content of the blood is increased and in large doses the respiratory centre loses its sensitiveness, and greater than normal percentage of CO_2 is required to bring about respiration.

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Morphine and its derivatives **depress** the excitability of the **respiratory centre.** Death takes place from paralysis of the centre and asphyxia. The cough centre is also depressed, in fact morphine, dionin and codeine reduce the sensibility of the cough centre in very small doses.

Bronchial muscles are slightly relaxed by therapeutic doses of morphine, but more powerfully by papaverine and narcotine. This relaxation is of value in giving relief in bronchial spasm. Unless there is nausea, the secretion of mucus is diminished, possibly due to suppression of cough and longer stay of the mucus in the bronchi, and consequent absorption of the water.

Nervous system.—The chief action of opium is on the nervous system. In small doses, it first **excites the higher faculties.** During this stage, with a few the excitement is a pure exaltation of feelings, the imagination being pleasantly excited with a sense of happiness and comfort and the animal tendencies are set free. With others, the intellectual activity is heightened, and they can concentrate their energies better on a particular object. But in the majority of cases, the excitability is not uniform. Depression soon follows excitement with lessened sensitiveness to pain and other disturbing factors thus promoting a dreamy, abstracted state of mind conducive to sleep. After waking, there is a feeling of headache and nausea. In this stage, the higher psychical centres are first depressed and then the lower ones. In fact opium acts on the cerebral centres in the reverse order of their development and forms an illustration of the "law of dissolution." Hearing, sight and cutaneous sensibility become blunted, and the sleeper feels no pain. Opium therefore resembles alcohol or chloroform in its effects on the central nervous system, but its action is directed more to the respiration and pain sensation, both of which are depressed in doses which have little effect on general consciousness. In fact morphine has a specific action in relieving pain in non-narcotic doses which it does by depressing the tracts by which the pain sensations reach the consciousness. If the dose is large, the excitement is only momentary or absent. Coma soon supervenes with a profound **depression** of the **cerebrum** and **reflex excitability.** The medullary centres are affected by morphine: the vagal and the vomiting centres are stimulated, while the respiratory and the cough centres are depressed. The oculo-motor centre is stimulated causing contraction of the pupil.

Because of the depressant effects on the brain morphine is valuable as a **pre-anæsthetic hypnotic** and is given prior to an operation to relieve the patient's anxiety and to render him indifferent to subsequent happenings. It also potentiates the action of volatile anæsthetics, and is often given with atropine to reduce salivary secretion.

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While depression of the central nervous system is marked in morphine poisoning in man, its effects on lower animals are peculiar. Thus in cat it causes wild delirium, restlessness and excitement for a considerable time before any signs of narcosis appear. In dogs the cardio-inhibitory centre is stimulated, and convulsion, vomiting and purging follow. As a rule relatively larger doses are required to elicit any effect in lower animals than in man.

Spinal cord.—Both morphine and opium, more particularly the latter increase the reflex excitability of the cord. In lower animals, e.g., frogs and cats, this is more marked and may be followed by convulsion of the strychnine type. In man the reflexes are depressed, but no muscular relaxation is noticed as happens after chloral or bromides. Sometimes however it produces convulsion in man, but how far this is due to asphyxia or to morphine is difficult to say.

Nerves and muscles.—The motor and sensory nerves are similarly affected. In the same way, it depresses the afferent nerves of the viscera. There is no complete loss of muscular power or irritability, for even in severe opium poisoning, a patient can be made to walk if supported.

Uterus.—Barbour has shown that in therapeutic doses it has no effect on normal uterine contraction of the animal. During labour it delays progress of the child and may be of use in checking threatening abortion from its sedative effect on the uterine muscle.

Temperature.—It reduces temperature by loss of heat from dilated peripheral vessels, diaphoresis, and partly from diminished movements by which less heat is formed.

Eye.—In morphine poisoning the pupils are contracted to a pin point, and they are contracted even in small doses. The effect lasts till asphyxia sets in when they are widely dilated. This effect disappears when the oculo-motor endings are paralysed by atropine, but it is not affected by cocaine which stimulates the sympathetic endings. The action is central, since when dropped into the eye or injected into the excised eye it has no effect. It has been suggested (Mayer and Gottlieb) that it depresses the inhibitory impulses which normally keep the oculo-motor tone in abeyance. The intra-ocular tension is increased.

Kidneys.—The secretion of urine is not affected by opium, although there is some retention of urine from spasm of the sphincter of the bladder in toxic doses, though it may also occur even in therapeutic doses. Morphine is found unchanged in the urine. There is a chance of morphine being reabsorbed from the bladder.

Skin.—Opium is a **diaphoretic**, acting by directly stimulating the sweat glands, and by dilating cutaneous vessels even in small doses. Before death there is copious perspiration due to asphyxia. It may cause itching and a rash.

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Secretion.—It diminishes every secretion of the body except that of the skin and the mammary glands.

It may cause poisoning through milk to suckling babies, and since it passes through the placental circulation to the fœtus, the latter may be killed in utero.

Elimination.—Morphine is excreted by the gastro-intestinal tract even when used hypodermically and continues to be found in the stomach all through the period of morphine action. Traces have also been found in the milk and sweat. The rest is oxidised into inactive oxydimorphine, some of which is excreted in the urine. The amount excreted with the urine is less at the beginning when most of the alkaloid is found in the stomach. Later it is increased.

Acute toxic action.—Poisoning by opium is very common in India especially in Bengal. It is chiefly suicidal, and is more frequent amongst the Indians. In most cases it is mixed with oil before swallowing. Excitement in such a case is very brief or none at all. Drowsiness and stupor soon follow. The patient may be roused at first, but soon passes into a profound coma, and no external stimulus can rouse him then. The **pupils contract to a pin's point**, surface becomes cold and clammy; face and lips livid; pulse very weak and slow; respiration slow, irregular and at the end stertorous; finally the patient dies from asphyxia. A few minutes before death, pupils dilate. P.M. appearances are like those of suffocation.

Antidotes.—If opium or morphine is swallowed, emetics, stomach-pump, or apomorphine $\frac{1}{10}$ to $\frac{1}{8}$ gr. subcutaneously. Potassium permanganate is a chemical antidote (1 gr. neutralises 1 gr. of morphine) and its solution (4 to 8 grs. in 4 to 8 ozs. of water) should be given at once if the quantity of poison is unknown or large, before emetics or washing. A weak solution of Liquor Potassii Permanganatis (1½ dr. to tepid water 1 pint) should be employed as a wash for the stomach. The special danger is the failure of respiration, therefore respiratory stimulants in the form of hot black coffee should be used. Atropine $\frac{1}{60}$ gr. should be given to excite the centre but in larger doses it tends to weaken the respiration. Strychnine $\frac{1}{60}$ gr. hypodermically, repeated every 2 or 3 hours for heart and lungs. Similarly, artificial respiration and inhalation of nitrite of amyl. Alternate cold and hot affusions, flagellations, or taps upon the forehead with finger-nails, sinapism, electricity, smelling salts to the nose, and making the patient walk to and fro, should be adopted to keep the patient awake. Oxygen inhalation is also recommended. The treatment is to be kept up for several hours until the danger is over. Some recommend washing the stomach now and then as opium is excreted in it, but that is unnecessary, as the quantity is infinitesimal and the exhaustion is rather overmuch.

Chronic toxic action or Morphinomania.—Persons soon get habituated to the use, and can consume large quantities. It is therefore necessary that the patient should remain ignorant of the drug. India, Turkey, Persia, and China are the principal countries where the drug is habitually indulged in. Morphinomania exists also in England. In India opium is either eaten or smoked. Moderate doses (5 to 20 grs.) daily do no harm, but *madak* and *chandu* smokers are a disreputable set. Moral depravity, emaciation, anæmia, muscular weakness, physical depression, feeble and small pulse, tremor, slight ataxy, loss of appetite, indigestion, sluggish bowels, insomnia, drowsy feeling, sexual impotence, amenorrhœa, small pupils, are the principal symptoms of morphinomania.

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Treatment.—*Gradual* reduction is the best plan. Tea, cocoa, ammonia may be given to ward off depression and collapse. Sometimes small doses of alcohol may be necessary. If an opium-eater be suddenly deprived of his accustomed dose of the drug, cerebral excitement, restlessness, pain in the stomach and a burning sensation in the back give great trouble. These symptoms are due to the formation in the tissues of an acrid irritating substance called "oxydimorphine." Hence the necessity for gradual reduction of opium so as to allow of the elimination of the product.

Diagnosis of opium poisoning.—This falls under the province of medicine. However, a few hints will enable the reader to form a correct diagnosis. (1) **From alcoholic coma.**—Take a careful *history*. *Smell of breath* may not help always, as the opium and alcohol may be taken together or one after the other, or some one may have given it later. *Pupils* are contracted in opium poisoning, and normal or dilated in alcoholic poisoning. *External stimulus* rouses the patient more readily in alcoholic coma than in opium poisoning. *Stomach-pump* will guide in some cases. (2) **Cerebral hæmorrhage.**—History. *Pupils* are unequally contracted, but if the hæmorrhage is in the pons, they may be contracted and render the diagnosis more difficult. *Paralysis* of limbs occurs on one side. *Temperature* generally falls in the beginning and then rises. (3) **Uræmia.**—*Coma* less profound. *Albumin* in the urine. Sometimes convulsions alternating with coma. Examine for *hypertrophy of the left ventricle*, *arterio-sclerosis*, and *retinal changes*. (4) **Diabetic coma**, by the breath and the presence of *sugar* and *diacetic acid* in the urine. (5) **Epileptic coma** after a fit, *coma* less profound, dilatation of pupils. Examine for *Babinski's sign*. (6) **Hysterical stupor** by its characteristic symptoms and history. (7) **Chloroform, ether, and carbolic acid poisoning**, by smell and other special symptoms.

Modifying influences.—Many circumstances modify the action of opium. (1) *Age.*—Children are more susceptible to poisoning. An infant under one year should not have more than ½ to 1 m. of the tincture. (2) *Sex.*—Women suffer more from after-effects than men. To a nursing mother it must be given with caution. (3) *Idiosyncrasy.*—Some cannot take opium without brain symptoms, such as insomnia or delirium, while others suffer from gastric irritation. The writer had to treat a woman in whom morphine ½ gr. given hypodermically produced fainting, vomiting, and collapse. (4) *Habit.*—Toleration is readily induced, when large doses become necessary to produce the desired effect and gradually lead to *opium habit*. The writer knew a person who used to take 40 grs. of morphine daily. (5) *Diseases.*—Acute painful diseases require larger doses. Subjects of Bright's disease cannot bear much opium, and it should be given to them with great caution, also to persons suffering from cardiac, pulmonary, and renal diseases, cerebral congestion, and alcoholism. (7) *Drugs.*—Chloral hydrate, potassium bromide, chloroform, etc., increase its soporific virtue, while belladonna removes constipation when given in combination.

Difference of action between opium and morphine.—Though the description of the pharmacology of opium given in these pages applies also to that of morphine, yet there are certain differences, which are detailed on page 177 :—

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Opium	Morphine
1. Preparations less soluble, slowly absorbed. Action slow, but more lasting.	Preparations more soluble, readily absorbed, action quicker, but not so lasting.
2. Its several constituents, such as thebaine, codeine, narcotine are convulsants.	Morphine not so in man.
3. Action variable on account of varying composition.	Action definite on account of definite composition.
4. Constipation, nausea, and indigestion more frequent.	Constipation, nausea, and indigestion less frequent.
5. Better diaphoretic.	Feeble or no diaphoretic.
6. Less sedative and less soporific.	More sedative and more soporific.
7. Greatly reduces the sugar of diabetic urine.	No appreciable effect.
8. Local action more marked on the intestines.	Less marked on the intestines.
9. Cannot be administered hypodermically.	Can be administered hypodermically.

Antagonists.—Atropine, caffeine, cocaine, physostigmine, and strychnine are antagonistic to some action or other of morphine. But the antagonism between morphine and atropine is given below in detail:—

	Morphine	Atropine
Real	1. Cerebral convolutions depressed.	Cerebral convolutions stimulated.
Real	2. Respiratory centre depressed.	Respiratory centre stimulated.
Real	3. Intestinal peristalsis depressed causing constipation.	Intestinal peristalsis regulated. No constipation.
Apparent	4. Stimulates the vagus centre and *slows* the pulse.	Depresses the vagus nerve endings and *quickens* the pulse.
Apparent	5. *Pupils contracted* through the effect on the pupillary centre.	*Pupils dilated* through the paralysis of the third nerve endings.
Apparent	6. *Diaphoretic* by specifically dilating the cutaneous vessels.	*Anhydrotic* through the terminal nerves in the glands.

Though morphine and atropine are not true antagonists, yet they are useful antidotes to each other in poisoning. The two drugs are however *synergists* in certain respects. Thus both first stimulate and then depress nervous centres, the vaso-motor centre and the sensory nerves. They are therefore partial antagonists and are used in combination to avoid certain untoward results of morphine without losing the useful effects. They are useful in combination in renal and hepatic colic, both of which relieve spasm and atropine obviates the nausea which follows the use of morphine alone.

Action of other opium alkaloids.—The important alkaloids are, morphine, narcotine, papaverine, codeine and thebaine. Of these morphine, codeine and thebaine are *phenanthrene derivatives*, while papaverine and narcotine are *iso-*

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quinoline derivatives. The latter group are depressants to the smooth muscles.

Papaverine is a powerful antispasmodic and relaxes all involuntary muscles specially when spasmodically contracted. Lowers blood-pressure from vaso-dilatation of the splanchnic area. The action on the central nervous system is between codeine and morphine. Small doses induce sleep, but large doses do not make it deeper. Not an analgesic. *Narcotine* resembles more papaverine in relaxing the plain muscles. *Thebaine* is not a depressant but is a convulsant like strychnine through its effect on the cord; it is however less active than strychnine.

Therapeutics

Externally.—Opium is chiefly used as a local sedative and anodyne. Hot poultices or fomentations containing opium or with laudanum sprinkled, are often employed to allay the pain of **pleurisy, rheumatism, peritonitis, lumbago, inflamed joint,** etc. *Earache* is relieved by laudanum mixed with equal amount of glycerin. Opium or morphine suppository, and the gall and opium ointment often allay the pain of **anal fissures** and **piles.** Opium injection *per rectum* relieves **rectal tenesmus, urethral spasms,** or **pelvic pains. Neuralgic pains** are better relieved when morphine is used hypodermically.

Internally.—Opium is a remedy *par excellence* for removing pain, subduing excitement and irritation, and inducing sleep.

Mouth and stomach.—Opium or morphine allays **gastric pain.** Thus it is very useful in ulcer, cancer, and gastritis produced by alcoholism. Morphine with bismuth markedly relieves gastrodynia with or without heartburn.

Intestines.—Of all the drugs we have for **diarrhœa** opium is the most valuable both in the acute, chronic and tubercular varieties. In **lienteric diarrhœa** where the half-digested food is simply swept down the canal by the excessive peristalsis, opium acts remarkably well. It is desirable to administer one or two doses of opium in diarrhœa or dysentery after the expulsion of the offending matters. It is usually combined with bismuth in diarrhœa and castor oil in dysentery. In the early stage of **cholera,** especially when preliminary diarrhœa is the prominent symptom, opium may be usefully employed, but not in the cold stage. In **typhoid fever** it serves a double purpose by controlling wakefulness and delirium and subduing diarrhœa. A rectal injection of starch and opium may sometimes relieve where the ordinary method of administration by the mouth has failed, especially in **dysentery.** It relieves **intestinal colic** caused by sharp aggravated contractions of the bowels.

Enema Opii (0·5 to 6 p.c. in mucilage of starch) 2 to 4 oz.

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is serviceable in various ways, by checking flux, subduing local irritation, pain and spasm of the rectum and neighbouring structures, and setting at rest the pelvic organs. A morphine suppository generally averts a rigor likely to follow catheterisation or abdominal operations. To soothe local pain, an ordinary dose is enough for rectal injection, but a large dose is required to induce sleep.

Heart and blood-vessels.—Opium, preferably morphine, is sometimes used in diseases of the heart. There can be no question that unmistakable relief is afforded by morphine injection in the **dyspnœa of heart disease** and of **blood-vessels**, and in **angina pectoris**. A single injection of $\frac{1}{6}$ gr. brings on refreshing sleep from which the patient wakes wonderfully revived; but it cannot relieve cardiac dyspnœa caused by the pressure of serous and dropsical fluid. If the kidneys are diseased opium is said to be contra-indicated. though Osler, Mackenzie and others recommended the administration of morphine in renal dyspnœa and uræmic convulsions, $\frac{1}{6}$ gr. subcutaneously. Belladonna may be usefully combined to counteract the depressing influence.

It is an excellent hæmostatic in internal hæmorrhage specially in **intestinal** and **pulmonary bleeding**. In the former, it is of special value because of its special action on the movements of the intestine; and in the latter, it not only slows the heart and reduces blood-pressure, but lessens cough, produces sleep, and removes mental anxiety.

Respiratory tract.—Opium relieves *cough* and should not therefore be prescribed indiscriminately. When the cough is harassing and frequent, without much expectoration and without any tendency to asphyxia or lividity, due to reflex irritation or from excessive irritability of the nerves, as in pleuritis, opium is justly and admirably indicated. But, when the act of coughing is only to empty the bronchial tubes of the abundant secretion, as in the bronchitis of the aged and infirm, or of the weak and young, opium is positively injurious; for it leads to inspissation and retention of the mucus. In **phthisis** where the tubercles press upon the nerves, and give rise to reflex cough, opium may be given with benefit. In the same way, by the local application of morphine to the throat, in the form of linctus and lozenges, many reflex coughs can be relieved. Sometimes it gives marked relief to the spasm in **whooping cough**; $\frac{1}{4}$ to 2 ms. of the linctus every hour, or $\frac{1}{50}$ gr. every 3 or 4 hours, according to the age of the child, should be continued until the whoop disappears. It should be given with great caution in **asthma**, lest it should create an opium habit, but instances are common where the habitual use of opium cured asthma. The sharp stitch of **acute pleurisy** or **pleuro-pneumonia** is relieved, as if by a charm, with a hypodermic injection of morphine. It may be used in the early stage of pneumonia

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to relieve pain and distress, but should be avoided in the later stage specially when there are signs of respiratory failure. A dose of Dover's powder often cuts short an attack of acute **coryza** and gives relief in influenza when taken with acetylsalicylic acid.

Nervous system.—(1) As a **hypnotic**, pure and simple, morphine is inferior to chloral hydrate, but for sleeplessness due to pain or irritation, it is a sovereign remedy. It is often used in the insomnia of acute diseases, in **mania** and **alcoholism**, and in the restlessness of visceral diseases. But the gradual tendency nowadays is in many of these diseases to combine it with chloral hydrate, either alone or with the addition of bromides, especially so in mania and delirium tremens. (2) Its superior value as an **anodyne** has been long recognised. A hypodermic injection of morphine ($\frac{1}{4}$ to $\frac{1}{3}$ gr.) relieves **biliary, lead** and **intestinal colics, sciatica, facial** and other kinds of **neuralgias, severe pleurodynia**. The pain of fractures, dislocations or other injuries, of acute rheumatism, dysmenorrhœa and malignant disease are only a few instances where opium or morphine can be most usefully employed. In short any pain, inflammatory or otherwise, is relieved by opiates. It is to be noted that sufferers from pain can consume large quantities without poisoning. (3) As an **antispasmodic**, opium is sometimes used in epilepsy, hysteria or chorea for various reasons.

It is valuable as a **pre-anæsthetic hypnotic** (*see* page 161) and is sometimes used to **prolong chloroform anæsthesia**, and when combined with scopolamine produces sufficient anæsthesia, to perform operations. For this purpose morphine $\frac{1}{6}$ gr. and scopolamine $\frac{1}{200}$ gr. is given in two injections. This combination has also been used during labour, the so-called "twilight sleep."

Cord.—The pains and spasms of certain diseases of the cord, such as **locomotor ataxy**, are subdued by the subcutaneous injection of morphine. Morphine is sometimes given to arrest the convulsions of **tetanus** and **strychnine poisoning**. A medical man by mistake took 40 ms. of liquor strychnine, and 80 ms. of liquor morphinæ put a stop to the threatening convulsion, he being a daily eater of morphine $\frac{1}{2}$ gr.

Kidneys.—As morphine is not rapidly eliminated by the diseased kidneys, it should be given with caution in Bright's disease, for instances have occurred where small doses have produced fatal results. But a hypodermic injection of $\frac{1}{4}$ gr. of morphine has occasionally been found to remove **uræmic insomnia, uræmic convulsions** and **uræmic** or **cardiac dyspnœa**, and one is justified in taking this risk under these conditions. As it reduces the sugar in diabetic urine, opium and codeine are employed in **diabetes mellitus**.

Skin.—As a diaphoretic, Dover's powder is used in a

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variety of diseases, such as cold, influenza and slight inflammatory conditions.

Uterus.—Opium is invaluable in arresting a threatening abortion. It must be given in large doses, laudanum in 20 or 30 ms., or the extract in 1 gr. doses every 3, 4 or 6 hours, as indicated. Sometimes a suppository or an enema succeeds better. It is also used to relieve after-pains.

Malaria.—It is a fact that opium-eaters are less liable to malarial poisoning, and they enjoy better health in malarial districts. Opium occasionally cures malarial fever where quinine fails, or the two drugs combined are more successful than either given alone. This effect is possibly due to *narcotine* which is used in chronic cases either alone or with quinine. The writer has seen a few cases of filarial fever checked by the habitual use of opium.

Mode of administration.—Opium and morphine can be administered by (1) the *mouth* as pill, powder and mixture; (2) *per rectum*, as suppository or enema; (3) *enepidermically*, as plaster; (4) *epidermically*, as liniment; (5) *hypodermically*, when the pain is very severe, such as colic or neuralgia.

Contra-indications.—It should not be used in

(*a*) œdema of the lungs, and Cheyne-Stokes breathing;

(*b*) inflammatory and congestive state of the central nervous system, *e.g.*, meningitis, fever, in overwork and in cerebral congestion with a tendency to apoplexy;

(*c*) acute dilatation (paralysis) of stomach or bowels; and *used with caution* in

(*d*) nephritis, especially when there is a tendency to uræmia;

(*e*) infancy and old age; and

(*f*) in all chronic painful diseases on account of the risk of formation of a habit.

CODEINA

Codeine. $C_{18}H_{21}NO_3,H_2O$

Syn.—Methylmorphine, U.S.P.

Source.—It is morphine methyl ether, an alkaloid obtained from opium, or prepared by the methylation of morphine.

Characters.—Colourless, translucent crystals, or a crystalline powder; odourless; taste, bitter. *Soluble* in 120 parts of water, readily in alcohol (90 p.c.), in 20 parts of ether, freely in chloroform.

B. P. Dose.—$\frac{1}{4}$ to 1 gr. or 0.016 to 0.06 grm.

CODEINAE PHOSPHAS

Codeine Phosphate. $C_{18}H_{21}NO_3,PO_4,H_2O$

Source.—The phosphate of the alkaloid codeine.

Characters.—Colourless, acicular crystals, or a crystalline powder; odourless; taste, bitter. *Soluble* in 3.5 parts of water, in 350 parts of alcohol (90 p.c.), sparingly in ether and chloroform.

B.P. Dose.—$\frac{1}{4}$ to 1 gr. or 0·016 to 0·06 grm.

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Non-official Preparations

1. **Linctus Codeinæ, B.P.C.**—Codeine Phosphate $\frac{1}{8}$ gr. in 1 dr. Syrup of codeine phosphate 50, citric acid 1·75, emulsion of chloroform 5, glycerin 16·50, mucilage of tragacanth *q.s.* to 100. *Dose.*—$\frac{1}{2}$ to 1 dr. or 2 to 4 mils.

2. **Codeinæ Hydrochloridum.**—A white crystalline powder, freely soluble in water. *Dose.*—$\frac{1}{4}$ to 1 gr. or 0·016 to 0·06 G.

3. **Codeinæ Sulphas, U.S.P.**—In long, glistening, white, needle-shaped, crystals or rhombic prisms, or as crystalline powder. Efflorescent. *Dose, U.S.P.*—0.03 gm. or $\frac{1}{2}$ gr.

4. **Apocodeinæ Hydrochloridum.**—A greyish powder soluble in water. Sedative and *increases intestinal peristalsis* by depressing sympathetic endings, therefore antagonises the action of atropine. 30 ms. of a 1 p.c. solution used hypodermically acts as a *purgative*. *Dose.*—$\frac{1}{10}$ to 1 gr. or 0·006 to 0·06 G.

5. **Dicodide.**—Dihydrocodeinone acid tartrate. Similar to dilaudide. Also makes the respiratory centre less sensitive to CO_2. *Dose.*—$\frac{1}{16}$ to $\frac{1}{12}$ gr. or 0·004 to 0·005 G.

6. **Syrupus Codeinæ Phosphatis, B.P. 1914.**—Codeine phosphate, 5 grm.; distilled water, 20 mil; syrup, q.s. 1000 mil. Strength $\frac{1}{4}$ gr. in 1 dr. *Dose.*—$\frac{1}{2}$ to 2 dr. or 2 to 8 mils.

Pharmacology

Internally.—Codeine is a feeble narcotic, because it does not depress the cerebral convolutions so actively as morphine, but it excites the cord more. It is therefore inferior to morphine in relieving pain and producing sleep. It does not produce nausea or vomiting, but causes constipation. It does not cause a habit, and is less depressing to the respiration than morphine, but it will relieve cough in doses insufficient to relieve pain. It is a great **paralyser of the visceral nerves**, for it has been found that after its administration, irritant poisons, such as arsenic, produce neither vomiting nor purging. Codeine decidedly excites the spinal cord producing muscular tremor and increased reflex excitability when used in slightly beyond the hypnotic doses. It **lessens the amount of sugar** in diabetes.

Therapeutics

Internally.—On account of its sedative influence on the visceral nerves, it soothes the **hacking cough of phthisis** and **visceral neuralgia**. Syrupus codeinæ in 1 to 2 dr. doses, alone or with syrup of virginian prune, is a good preparation for allaying cough. Sometimes it is used with advantage in **insomnia** due to pain in some peripheral regions, when it should be given in 1 or 2 gr. doses, every 4 or 6 hours, till sleep comes on. But its chief use is in the treatment of **diabetes mellitus**, in which case it can be given in the form of a pill. The phosphate being more soluble than the alkaloid can be used in a mixture. It is highly efficient in abdominal and pelvic pain, specially when ovarian in origin.

Apocodeine resembles apomorphine in its action, but is

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a better expectorant and less efficient emetic than the latter. 30 ms. of a 1 p.c. solution is used in bronchitis, and the same amount when used hypodermically acts as a purgative.

DIAMORPHINAE HYDROCHLORIDUM

Diamorphine Hydrochloride. $C_{21}H_{23}NO_5,HCl,H_2O$

Syn.—Heroin Hydrochloride: Diacetyl-morphine Hydrochloride.

Source.—The hydrochloride of an alkaloid obtained by acetylation of morphine.

Characters.—A white, crystalline powder; taste, bitter. *Solubility.*—1 in 3 parts of water, 1 in 11 parts of alcohol (90 p.c.).

Incompatibles.—Acids and alkalies which decompose it.

B.P. Dose.—$\frac{1}{2}\frac{1}{0}$ to $\frac{1}{8}$ gr. or 0·0025 to 0·008 grm.

Non-official Preparations

1. **Elixir Diamorphinæ et Pini Co., B.P.C.**—Each dr. contains $\frac{1}{3}\frac{1}{6}$ gr. diamorphine hydrochloride, 1½ ms. oil of pine, and $\frac{5}{1}\frac{}{8}$ gr. terpin hydrate. *Dose.*—½ to 1 dr. or 2 to 4 mils.
2. **Elixir Diamorphinæ et Terpini cum Apomorphina, B.P.C.**—Contains $\frac{1}{6}\frac{}{0}$ gr. heroin hydrochlor., $\frac{5}{1}\frac{}{8}$ gr. terpin hydrate and $\frac{1}{3}\frac{}{2}$ gr. apomorphine hydrochloride in 1 dr. *Dose.*—½ to 1 dr. or 2 to 4 mils.
3. **Linctus Diamorphinæ cum Ipecacuanha, B.P.C.**—Contains $\frac{1}{6}\frac{}{0}$ gr. heroin hydrochlor, ¾ m. liquid extract of ipecac., in 1 dr., with hyoscyamus, and syrup of tolu. *Dose.*—½ to 1 dr. or 2 to 4 mils.
4. **Glycaphorm.** *Syn.—Glycerole of Heroin.*—Contains $\frac{1}{1}\frac{}{8}$ gr. of heroin hydrochlor. in each drachm of a vehicle consisting of glycerin 3, syrup of roses 4, water 1. A useful linctus. *Dose.*—1 to 2 drs. or 4 to 8 mils.

Pharmacology and Therapeutics

Heroin resembles morphine in its general action, which it has replaced in the treatment of cough, especially the dry hacking **cough of phthisis.** It is a depressant to the respiration, which is rendered slower but deeper, but it does not interfere with gas exchange, and is used to stop irritable **cough.** It is about five times more depressant than morphine, but less so to sensory nerves and not so constipating. A hypodermic injection often relieves a fit of **asthma.** For the relief of cough it is generally used in the form of linctus. It is liable to produce a 'habit' and causes suppression of urine, and has no advantage over morphine or codeine.

CANNABIS INDICA

Indian Hemp. (Not official)

Syn. I.V.—*Ganja*, Beng., Hind.

Source.—The dried flowering or fruiting tops of the pistillate plants of *Cannabis sativa*, grown in India; from which no resin has been removed.

Composition.—(1) An active *Resin*, the chief constituent of which is *Cannabinone*, $C_{21}H_{26}O_2$. (2) A *Volatile Oil.* Fat, wax, etc.

Incompatibles.—Water and watery infusions precipitate the resin.

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Non-official Preparations

1. **Extractum Cannabis.**—A rich green, soft resinous extract. *Dose.*—¼ to 1 gr. or 0·016 to 0·06 grm.

2. **Tinctura Cannabis.**—1 in 20. 22 ms. contain 1 gr. of extract. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.

3. **Cannabinæ Tannas.**—A brownish powder. In *dysmenorrhœa, menorrhagia,* and as a *hypnotic* in nervous insomnia. *Dose.*—4 to 8 grs. or 0·25 to 0·5 grm.

Pharmacology of Cannabis Indica

Internally.—In small doses it **sharpens the appetite,** which becomes sometimes so ravenous that it cannot be appeased by food. It also **promotes digestion** and causes constipation. If indulged in for long it may cause loss of appetite and gastric derangement. It is slowly absorbed by the small intestine and produces its effects within half an hour. It **relieves spasm** of the **intestine.**

Nervous system.—Its chief action is on the cerebrum and resembles in many respects that of alcohol or opium, but is uncertain owing to variation in strength and to individual peculiarities. When smoked the effects are almost instantaneous. In small doses, either smoked or taken by the mouth, it causes pleasurable sensations with gay, joyful and exalted ideas and a refreshed feeling, specially after bodily fatigue. In fact it is often smoked by some people to enable them to undergo physical exertion without appreciation of fatigue or exhaustion. Ganja smoking is almost universal with certain classes of *sadhus* and *mendicants,* and it is said it helps them to forget all about their worries and privations of the outside world, and concentrate their mind in an agreeable manner to their devotion. Under its influence the knowledge of time and personality is lost and the drugged man feels that he is enjoying the pleasures of life for hours together, although in reality it is only for a few minutes. If continued it causes intoxication and loss of self control. The drugged man becomes very talkative and jovial, and laughs at every thing, whereas a sedate person becomes more sociable, has less control over himself, and eventually passes into a sort of waking delirium. The delirium, generally noisy and restless, is accompanied by muscular excitement, and is followed by sleep which is attended with delightful and erotic dreams. It is therefore an **exhilarant, deliriant** and **hypnotic.** Sometimes there is considerable amount of heaviness in the head and the patient feels "a sensation as of the brain boiling over and lifting the cranial arch." In large doses it induces a sort of catalepsy, followed by coma and death from cardiac failure. Excessive smoking of ganja, specially by beginners may cause mental derangement and even insanity.

The **sensory nerves** are **paralysed** and there is tingling and anæsthesia of the skin. The muscular sense is also lost,

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and if pain is present is abolished or at least reduced. It is an **anodyne** but less so than opium or belladonna.

Heart and circulation.—Its action here is very uncertain. The pulse may be quickened or slowed depending upon excitation or narcosis.

Respiration is not affected. The breathing becomes hurried during the stage of excitement. The pulse is not altered when taken as a drink, but becomes slow during narcosis.

The secretion of urine is slightly increased, but prepared *bhang*, which is used as a drink, causes copious **diuresis.**

In the form of *ganja*, hemp is largely smoked, and the leaves are used by powdering it and mixing with aromatics, sugar, cardamom and milk, and the preparation is then known as *bhang*, *sidhi*, or *sabji*. *Charas* is of a dark green or brown colour and contains resins which exude from the leaves, and is as a rule smoked with tobacco, and is a powerful narcotic. The leaves are also used in the preparations of different kinds of sweets and pastries, and the prepared bhang is also taken as ice-creams. They all produce the same effects on the central nervous system. *Hashis* is a confection and contains in addition to the leaves and resins, opium, poppy seeds, datura seeds, cloves, anise, sugar, butter, milk, etc.

Therapeutics of Cannabis Indica

Externally.—Mixed with linseed meal (1 in 4), hemp in the form of poultice allays the irritation and pain of inflamed **piles** and **fissures.** The dry leaves warmed may be used as fomentation for the same purpose.

Internally. **Gastro-intestinal tract.**—As an appetiser and stomachic tonic it is valuable in **dyspepsia** and **dyspeptic diarrhœa,** and relieves pain and spasm in some forms of dysentery specially when combined with small doses of castor oil. It soothes the pain of gastralgia and corrects the griping of purgatives.

Nervous system.—As an *analgesic* it was largely used in migraine, but is not much used now being replaced by the drugs of the phenacetin group. It is occasionally used with benefit in continuous **headaches,** specially those occurring at the menopause, or due to worry and fatigue. As a hypnotic it is rarely used now although Sir Russell Raynolds strongly recommends the extract ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) in senile insomnia. As an anodyne antispasmodic, the tincture or the extract may be used in **intestinal, biliary** and **renal colics, spasm of the bladder** and **chordee.** Its beneficial effects in **tetanus** has long been recognised.

Genital organs.—In menorrhagia, spasmodic and nervous dysmenorrhœa and ovarian irritation, it not only relieves the pain, but seems to act favourably on the uterine muscular fibres.

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(*b*) **Bromide and Chloral Group**

POTASSII BROMIDUM

Potassium Bromide. KBr

Source.—Obtained by the interaction of ferrous bromide with potassium carbonate. Contains not less than 99 p.c. of pure potassium bromide.

Characters.—In colourless, transparent or opaque, crystals, or a white granular powder; taste, saline. *Solubility.*—1 in 2 of water, 1 in 200 of alcohol (90 p.c.).

Incompatibles.—Solution containing free chlorine or free acids, spirit of nitrous ether if acid, mercury, silver salts, and strychnine.

B.P. Dose.—5 to 30 grs. or 0·3 to 2 grm.

SODII BROMIDUM

Sodium Bromide. NaBr

Source.—Prepared in the same manner as potassium bromide, sodium carbonate being used in place of potassium. Contains not less than 99 p.c. of pure sodium bromide.

Characters.—In small, white transparent or cubic crystals, or a white granular powder, somewhat deliquescent, inodorous; taste, saline. *Solubility.*—1 in 1.5 of water, 1 in 16 of alcohol (90 p.c.).

B.P. Dose.—5 to 30 grs. or 0·3 to 2 grm.

ACIDUM HYDROBROMICUM DILUTUM

Dilute Hydrobromic Acid

Source.—Obtained by the interaction of bromine and sulphurous acid. Contains not less than 10 p.c. w/w of HBr.

Characters.—A clear, colourless and odourless liquid. Sp. gr. 1.072 to 1.075.

B.P. Dose.—15 to 60 ms. or 1 to 4 mils.

Non-official Preparations and Derivatives

1. **Ammonii Bromidum.**—In small colourless crystals; saline pungent taste. Soluble in water. *Dose.*—5 to 30 grs. or 0.3 to 2 G.

2. **Liq. Bromidi Compositus, B.P.C.** *Syn.—Bromidia.*—1 dr. contains 15 grs. of each of Chloral Hydrate and Pot. Bromide. Chloral Hydrate 27.50, Ext. Cannab. Ind. 0.23, Tr. Aurantii 12.50, Ext. Hyoscyam. Liq. 1.38, Glycerin 18.75, Pot. Bromide 27.50, add Water to 100. *Dose.*—½ to 2 drs. or 2 to 8 mils.

3. **Bromoform.**—It is tribromomethane, contains about 4 p.c. alcohol. A colourless, volatile, sweet liquid, with an agreeable odour. Soluble in chloroform, ether, and slightly in water. Most efficacious in *whooping cough. Dose.*—½ to 2 ms. or 0·03 to 0·12 mil.

4. **Brometone.**—*Tribrom-tertiary Butyl Alcohol.*—White crystals containing about 77 p.c. bromine. Hypnotic, analgesic and antiseptic. Useful in sea-sickness. *Dose.*—5 grs. repeated 2 or 3 times in 24 hours.

Pharmacology of Bromides

Externally.—Bromides have no action on the unbroken skin, but on the denuded surface a concentrated solution acts as an **irritant.** The fumes of bromine are so irritating to the respiratory tract that they cannot be inhaled.

Internally. **Alimentary canal.**—Either in concentrated solution applied to the throat or in repeated large doses given by the mouth, bromides diminish the sensibility and

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the reflex excitability of the fauces. Tickling the pharynx then no longer tends to excite vomiting even though the tactile sensation may remain. The bromides are readily absorbed by the gastro-intestinal mucous membrane and circulate as sodium bromide. Large doses in concentrated solutions produce nausea, vomiting and gastralgia by their local salt action.

Heart and circulation.—In therapeutic doses there is no essential effect on the heart and circulation, but in cardiac neurosis the bromides steady and quiet the heart's action through their general sedative effect. It is only when potassium bromide is used intravenously that the heart is depressed like other potassium salts.

Respiration is only slightly depressed and becomes slower. This however is not more than is observed in natural sleep. The coughing reflex is diminished.

Nervous system.—The chief action of bromides is on the entire nervous system, which is **moderately depressed** and owing to slow excretion this depression can be maintained for a long period without any effect on the vital centres or the medulla. This fact makes it so valuable in the treatment of epilepsy where it is necessary to keep the central nervous system depressed for a prolonged period. In their progressive action on this system, they do not follow the "Law of Dissolution" but the highly developed functions and the lower and the spinal ones are all affected at the same time. Used for long, even in small doses, bromides make the patient dull and apathetic with impairment of the power of concentration. They **lessen the functional activity of the brain.** The sensibility, excitability emotional activity are all diminished, thereby inducing a state most favourable for sleep. They cause sleep by rendering the brain less sensitive to external influences. The sleep is not always refreshing and owing to the slow excretion is followed by drowsiness and weariness. They also depress the motor area and block the passage of sensory impulses along paths which connect the motor centres, though the paths connecting cerebral centres to the motor cells remain intact.

The great vital centres are more or less depressed by large doses, and there is considerable impairment of the reflex excitability, so that larger doses of strychnine than usual are required to elicit convulsion. They diminish the irritability of the mucous membranes, the earliest and most marked being the throat which can be touched and examined without inducing reflex vomiting, although sensation of touch remains unimpaired. After large doses complete anæsthesia may be induced. Cutaneous sensation is also impaired by comparatively small doses, not from any peripheral action but from central effect.

Muscles.—The bromides not only impair the activity of

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the muscles by their action on the motor-cells and reflex centres, but by their direct influence on the muscles themselves. They may be paralysed to such an extent that no convulsions can be produced by poisoning with strychnine. Therefore they are powerful **antispasmodics.**

Genitals.—Bromides decidedly lessen virility and if continued long the sexual passion, due either to its action on the brain, or diminished reflex activity.

Elimination.—Inspite of the fact that elimination of bromide by the kidneys begins soon after administration, the process is slow and traces have been found 20 days after cessation of administration. Owing to this fact certain saturation of the organism results. During a long course of bromide treatment the blood always contains bromides and the chlorides are correspondingly diminished. They also partially replace chlorides in other tissues, accumulating in the largest amounts in those organs which normally are richest in chlorine. For instance, hydrobromic acid appears in gastric juice. The elimination of bromides depends upon the amount of sodium chloride. Conversely a salt-free diet retards their excretion and helps saturation in the body. Prolonged use gives rise to a form of rash (bromide rash) probably due to sensitisation of the skin, and mostly disappear on stoppage of the drug.

Bromides are eliminated by the intestinal and bronchial mucous membrane, skin, saliva and milk. Many think they depress the sensibility of the fauces during excretion.

Acute toxic action.—Acute poisoning is rare, but if ½ to 1 oz. is swallowed, weakness, frontal headache, reduction of pulse rate, insensibility, aphasia, amnesia are the chief symptoms. Recovery as a rule takes place unless œdema of the lungs supervenes.

Chronic toxic action or "Bromism."—The symptoms of chronic poisoning are observed after prolonged use of bromides, as happens in the treatment of epilepsy. The earliest of them is a rash resembling acne, which appears mostly on the face and back and sometimes may lead to boils. Mental dullness, anæmia, muscular weakness, general prostration, and dulling of cutaneous sensibility and that of the pharynx. These are followed by diminution of sexual power, and a general lowering of vitality and vigour.

In some the symptoms are more of the *psychotic type.* There may be restlessness, hallucination and delusion, disorientation and a sense of persecution. In severe cases respiration becomes depressed, slow and laboured, pulse feeble and eventually fever comes in followed by death.

Treatment.—As a rule stoppage of the drug is sufficient in the early stage. Administration of sodium chloride helps elimination and should be given either by the mouth in 15 gr. doses three times a day, or in urgent cases, physiological saline solution intravenously (100 to 400 c.c.) daily. Caffeine and strychnine should be given to counteract depression.

Therapeutics of Bromides

Internally.—Bromides are chiefly used therapeutically as **sedatives** in hypersensitive state of the nervous system.

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They are also used as **hypnotics** to promote sleep, but are not of value when sleeplessness is due to painful conditions. Bromides may therapeutically be used:

1. As a *hypnotic* they are very efficacious in sleeplessness caused by worry, overwork or mental strain. They are of no use when sleeplessness is due to pain. Sometimes however bromides fail to produce sleep and give rise to much depression and confusion. In delirium tremens, mania, acute inflammatory and febrile diseases, cerebral congestion, night screaming of children, nightmare of children and adults, bromides may be used with the greatest benefit either to induce sleep or to allay irritability.

2. *To allay slight pain* which is keenly felt on account of the hypersensitiveness of the nervous system.

3. *To lessen excitability* bromides are very effective in **irritability** of temper, **nervous excitability** of women either during the latter months of pregnancy or the change of life, hysteria, hypochondriasis, etc.

4. *To prevent convulsions* they are used in infantile convulsions, epilepsy, puerperal eclampsia, hysteria, chorea, tetanus, and strychnine poisoning. In epilepsy their efficacy is more marked in *grand mal*, producing little or no effect in *petit mal*. In this disease large doses are required if any physiological effects are to be obtained, and must be continued for prolonged periods. No definite results are obtained until the body is saturated with bromide, and this is helped by keeping the patient on a salt-free diet. The regulation of the dose is an important factor. Commencing with a dose of 10-15 grs. given three times a day it should be slowly increased till the maximum is reached, as judged by the patient's condition, *i.e.*, cessation of fits. This dose should be maintained for some time and then reduced in the same manner. The treatment should be continued as long as necessary, the aim being to find out the optimum dose that will keep away the fits. A few patients do not show any improvement, and in some the fits return with the stoppage of treatment. It should be noted that although other compounds may contain bromine, e.g. bromoform, they are not of any value in epilepsy since they do not liberate bromine ion in the body. Recently its use has been partly replaced by luminal.

5. *To lessen sexual excitability*, as in chordee and nymphomania.

6. As a *sedative in all spasmodic conditions*, such as pertussis, asthma, hiccough, laryngismus stridulus, etc.

7. As a *cardiac sedative* in nervous arrhythmias.

8. *To check reflex or central vomiting*, as sea sickness, etc.

9. *As a preliminary anæsthetic*, sodium bromide is used 25 to 40 minutes before operation. Twelve to 15 grm. dissolved in 25 c.c. of distilled water is introduced into a vein

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and the operation performed under small doses of ether to maintain full anæsthesia.

The salts most commonly used are potassium or sodium bromide, and as above mentioned it is in large and toxic doses that the potassium ion has any special depressing effect.

Potassium bromide and dilute hydrobromic acid lessen the disagreeable effects of quinine, salicin and salicylates. The usual practice is to order 2 ms. of the acid for every grain of quinine. Bromide rash is checked by keeping the skin clean and using small doses of arsenic.

Prescribing hints.—Bromides may be administered by the mouth or rectum. Their taste is fairly well disguised by the liquid extract of liquorice, milk or beer. For an enema they may be dissolved in gruel or mucilage. Their efficacy is greatly enhanced if the patient is restricted to vegetable food and a salt-free diet. The hypnotic effect of the bromides may be greatly increased if they are given with chloral hydrate, morphine or hyoscyamus. In some cases of *insomnia* bromidia may be used with great advantage. Anæmic persons cannot bear a protracted course of bromide treatment. Children, even very young ones, bear bromides well. In *whooping cough* bromoform is sometimes more beneficial than the bromides. Bromides should not be prescribed with strychnine or other alkaloids in a mixture, as they throw down alkaloidal precipitates, especially if the solution is concentrated.

CHLORALIS HYDRAS

Chloral Hydrate. $C_2Cl_3H_3O_2$

Source.—Obtained by the addition of water to chloral, produced by the action of dry chlorine on ethyl alcohol.

Characters.—In colourless, non-deliquescent crystals. Odour pungent but not acrid. Taste, pungent, bitter. Volatilises slowly on exposure to air. *Solubility.*—Freely in water, alcohol (90 p.c.), ether, and in 3 parts of chloroform.

Incompatibles.—Alkaline substances which liberate chloroform.

B.P. Dose.—5 to 20 grs. or 0.3 to 1.2 grm.

Non-official Preparations and Derivatives

1. **Chloral Camphoratum, B.P.C.**—Each equal amount. Rub together in a warm mortar until liquefied. An effective local anodyne.

2. **Syrupus Chloralis, B.P. 1914.**—Chloral hydrate 200 grm., water 200 mil., syrup to 1000 mil. Each fluid dr. contains about 11 grs. of chloral hydrate. *Dose.*—30 to 120 ms. or 2 to 8 mils.

3. **Dormiol.** *Syn.—Amylene Chloral.*—A colourless liquid with camphoraceous odour. A good *hypnotic* in mental diseases. Used in *night sweats of phthisis.* Does not depress the heart and respiration. *Dose.*—5 to 50 ms. or 0.3 to 3.5 mils.

4. **Butyl-chloral Hydras.**—In pearly white trimetric laminæ, with a pungent, acrid odour and an acrid taste. Action similar to chloral hydrate, supposed to be specially valuable in neuralgia of the 5th nerve. *Dose.*—5 to 20 grs. or 0.3 to 1.2 grm.

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5. **Glucochloral, B.P.C.** *Syn.—Chloralose.*—A hypnotic, resembles more morphine than chloral. Produces increased reflexes and sometimes convulsion, specially when large doses are given. Heart is not affected nor the respiration unless given in large doses. *Dose.*—3 to 10 grs. or 0.2 to 0.6 grm.

PHARMACOLOGY

Locally chloral is an **irritant** to the skin and when used in a concentrated solution may even cause **vesication.** It is an **antiseptic.**

Internally.—Chloral is an irritant to the stomach and in concentrated solution causes **nausea** and **vomiting.** Given freely diluted no such effect is observed. It is readily absorbed and carried to the central nervous system where it is taken up by the cells. It is reduced in the body into trichlorethyl alcohol, which also acts as a hypnotic.

Heart and circulation.—A moderate dose of chloral (10 to 20 grs.) in a healthy adult rarely causes any circulatory changes except that the heart is rendered slow, but this is not more than is found in natural sleep. In common with all narcotics containing a halogen derivative, it depresses the heart and finally arrests it in diastole, but this effect is only observed when the dose is above the therapeutic limit. This is due to its direct action on the cardiac muscle. The blood pressure is not affected in ordinary therapeutic doses, but there is some flushing of the skin from dilatation of the cutaneous vessels, and an erythematous rash. In large doses, or in poisoning, the pressure falls from diminished cardiac output and depression of the vaso-motor centre causing dilatation of the vessels, when the pulse becomes slow, feeble and intermittent.

Respiration.—In moderate doses no effect on respiration is observed, but in toxic doses the breathing becomes slower, shallower and irregular, and finally stops with the simultaneous arrest of the heart. This action is due to the effect of the drug on the respiratory centre.

Temperature.—Chloral hydrate tends to lower the body-heat, and in toxic doses there is a marked **diminution** of the **temperature,** due to dilatation of the cutaneous vessels and diminished production of heat from muscular relaxation and possibly to diminished activity of the heat regulating centre.

Cerebrum.—In moderate doses (1 to 2 gms.) it induces within ten to fifteen minutes a sort of soothing drowsiness followed by refreshing sleep indistinguishable from natural slumber. The sleep generally lasts from 5 to 8 hours without producing any unpleasant after-effects, such as, headache, drowsiness, confusion or sickness. Large doses cause prolonged sleep which is deeper, and although no complete anæsthesia is produced, pain is less felt and the reflexes are lessened. Still larger doses produce stupor and coma with complete muscular relaxation leading to asphyxia from paralysis of respiration. Before death the pupils are powerfully

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contracted to pin point. It induces sleep by depressing the sensory or receptive functions of the brain. And since the sleep is induced by dulling of the perceptions, acute pain may prevent sleep after chloral. In fact chloral has no effect in relieving pain like opium. The motor areas of the brain cortex are rendered less irritable which eventually fail to react to electrical stimulation.

Spinal cord.—In ordinary hypnotic doses the spinal reflexes are not affected. In large doses they are first depressed and then paralysed before the failure of respiration. This effect on the spinal reflexes is more marked than morphine.

Kidneys.—It is excreted by the urine in combination with glycuronic acid which reduces Fehling's solution and therefore it was thought that chloral caused glycosuria. Large doses cause nephritis and hæmaturia.

Absorption and elimination.—It is absorbed from all mucous surfaces and excreted with the urine as non-toxic trichlor-ethylglycuronic acid (urochloralic acid). It has less tendency to cumulative effect. A portion is eliminated unchanged. It escapes chiefly by the kidneys and partly by the lungs and skin.

Acute toxic action.—Acute poisoning is rare. The writer has seen only one case—a habitual drinker who died after taking 80 grs. The symptoms are profound sleep merging into deep coma; lividity of the face; pallor; cold sweat over the forehead and head; slow, laboured, and afterwards shallow and feeble breathing; frequent, feeble, and irregular pulse; *marked fall of temperature*, which may be so great as alone to cause death (Brunton); pupils contracted and absolute muscular relaxation. Death takes place from paralysis either of the heart or of the respiratory centre.

Antidotes.—Emetics or pump. Friction; external warmth; stimulants, such as ammonia, ether, etc.; sinapisms over the chest and nape of the neck; electricity; atropine, strychnine, caffeine hypodermically. The patient if he can be roused should not be allowed to sleep, a pint of strong coffee may be introduced into the rectum as recommended by Murrell.

Chronic toxic action or Chloralism.—Craving for chloral is soon generated in those who are addicted to its use. Gastro-intestinal disturbance; cutaneous eruption, such as erythema, pustules, vesicles, etc.; bodily and mental weakness; sudden flushing, dyspnœa and palpitation are prominent symptoms Death often results from an over-dose. The best treatment is the gradual withdrawal of the daily dose with generous diet, fresh air, tonics and nervine sedatives such as hyoscyamus.

Physiological antagonists.—Atropine, strychnine, physostigmine, picrotoxin.

THERAPEUTICS

Externally.—As a *local anodyne* Chloral Camphor or Chloral c. Menthol may be painted over superficial **neuralgic areas**, and applied within **carious painful teeth.** The efficacy of any of these combinations may be greatly augmented by the addition of cocaine.

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Internally—As a *pure and simple hypnotic* it is unrivalled in sleeplessness due to worry, overwork or old age, but not to pain. In doses of 15 to 20 grs. it induces a refreshing sleep, which thus obtained not infrequently leads to the repeated use of the drug and thereby induces the chloral habit. It is very efficacious in febrile insomnia. In fatty degeneration of the heart a hypnotic like paraldehyde, barbitone or medinal should be used, as they do not contain any chlorine molecule. In other affections of the heart, chloral may be used safely, and is often of great value as a hypnotic. It is a most valuable remedy for **delirium tremens**. In combination with bromide of potash it will often check the disease in the early stages. The method of administration is as follows :—During the day 20 grs. of sulphonal, dissolved in a glass of warm milk or broth should be given every 3 hours, then at 8 p.m. administer 20 grs. of chloral with 20 grs. of potassium bromide and repeat the dose every 2 hours as long as the patient remains awake. If this produces sleep, the patient may wake up perfectly cured.

Because it depresses the motor area of the cord it is extensively used in several **convulsive diseases** of children and adults, *viz.* eclampsia, tetanus, strychnine poisoning, hydrophobia, tetanus neonatorum, etc., specially in combination with bromides. The addition of a few drops of the tincture of Indian hemp to the chloral and bromide mixture gives very satisfactory results in tetanus. Many other **spasmodic affections**, such as chorea, asthma, whooping cough, paralysis agitans, spasmodic intestinal colic are benefited by it. It is an excellent drug for lessening the **rigidity** of the **os** and other soft parts during the first stage of labour without affecting the uterine contractions.

As a *general anodyne* it is far inferior to morphine. The difference between the actions and uses of chloral hydrate and morphine is given below :—

Chloral Hydrate	Morphine
1. A quicker, and a more refreshing hypnotic.	A slower, and a less refreshing hypnotic.
2. No after-effects, such as headache, depression, and sickness (sometimes heaviness or sleepiness only).	Always headache, confusion, and narcotism.
3. No constipation. No gastro-intestinal derangement in medicinal doses.	Constipation common and sometimes nausea.
4. Cannot relieve excessive pain nor induce sleep in insomnia caused by it.	Relieves pain and induces sleep in insomnia caused by it.
5. Cannot relieve reflex cough, but can relieve convulsive diseases.	Relieves reflex cough, but not so useful in convulsive diseases.

Caution.—It should be given with caution to old, gouty,

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rheumatic, hysterical, delicate, and otherwise constitutionally weak persons. It should not be given to confirmed drunkards, except when absolutely necessary for the treatment of delirium tremens. It is contra-indicated in threatened failure of circulation, pneumonia, acute nephritis and gastric irritation.

Prescribing hints.—The aromatic syrup or syrup of ginger best covers its pungent taste. On account of its irritant effect it should be used freely diluted, and should not be used either in the form of tablets or pills, as when used in these concentrated forms it may irritate the stomach and the intestine. It may be given by the rectum and is more effective than when given by the mouth. When prescribed with alkalies they decompose it and liberate chloroform. With camphor and menthol it forms an oily liquid.

CHLORALFORMAMIDUM

Chloral Formamide. (Not official)

Syn.—Chloralamide.

Source.—Obtained by the direct combination of formamide with anhydrous chloral.

Characters.—Colourless, inodorous, lustrous crystals. Taste, slightly bitter.

Solubility.—1 in 21 of water, freely in alcohol (90 p.c.), solution neutral to litmus.

Dose.—15 to 45 grs. or 1 to 3 grms.

Pharmacology and Therapeutics

Chloralamide resembles chloral in its action with this advantage, that formamide, which is a stimulant, counteracts the depression of the circulation produced by chloral alone. It is less irritant to the stomach and kidneys than chloral, but is absorbed more slowly and after absorption is converted into chloral and is excreted partly as urochloralic acid. Chloral-formamide may therefore be used as a **nervous sedative** wherever chloral is indicated. It takes about half to three-quarters of an hour to induce sleep, and some hold that it not only produces sleep but relieves pain. It is therefore of value in **neuralgia** and in relieving the pains of **locomotor ataxy.** Combined with bromide it has yielded good results in **sea-sickness.** It is incompatible with alkalies and should not be given with hot liquids.

CHLORBUTOL

Chlorbutol. $(CH_3)_2C(CCl_3).OH$

Syn.—Chloretone.

Source.—It is trichloro-*tert.*-butyl alcohol with a variable amount of water of crystallisation. Prepared by heating a mixture of acetone and chloroform with potassium hydroxide.

Characters.—Colourless crystals; odour and taste, characteristic, musty, and somewhat camphoraceous. Volatile at ordinary temperatures. *Soluble* in 125 parts of water, in 1 part of alcohol (90 p.c.), readily in ether and chloroform; in 10 parts of glycerin, and in volatile oils.

B.P. Dose.—5 to 20 grs. or 0.3 to 1.2 grm.

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Pharmacology and Therapeutics

The action of chlorbutol resembles that of chloral except that it does not irritate the stomach. It is an **antiseptic** like chloral but acts as a local **anæsthetic** by paralysing the sensory nerve endings. An ointment with boric acid is used to soothe irritation and pain in **burns** and **scalds**, and to relieve **pruritus**, and an ointment or suppository is valuable in **inflamed piles**. Dissolved in liquid paraffin (1 p.c.) it is used as a spray in rhinitis, nasal catarrh, and sorethroat, and may be combined with menthol and camphor.

Being a gastric sedative, small repeated doses, either alone or combined with fractional doses of calomel, act as **antiemetic** and check vomiting of pregnancy, sea-sickness, post-anæsthetic vomiting and vomiting of cholera. It is a **hypnotic** in 10 to 15 gr. doses and is useful in nervous excitability; while as an **antispasmodic** it is useful in hiccough, whooping cough, epilepsy and tetanus. In tetanus it may be given in 2 grm. doses dissolved in olive oil 4 grms. by rectal injection.

Because of its antiseptic property it is used to preserve organic substances from decomposition. In fact it is added to adrenaline chloride solution for preservation.

The usual method of administration is in powders, cachets, or gelatin capsules. As it volatilises even at the ordinary temperature slowly, the powders should be dispensed enclosed in tinfoils and in stoppered bottles. When given in mixtures it should be suspended with acacia or tragacanth.

(*c*) Aldehyde Alcohol Group

PARALDEHYDUM

Paraldehyde. $C_6H_{12}O_3$

Source.—A product of the polymerisation of acetaldehyde.

Characters.—A clear, colourless liquid; odour strong, characteristic; taste, disagreeable. Sp. gr. 0.998 to 1.000. *Solubility.*—1 in 9 of water and with all proportions in ether and alcohol.

B.P. Dose.—30 to 120 ms. or 2 to 8 mils.

Pharmacology

Paraldehyde is readily absorbed, and manifests its action chiefly on the cerebrum, producing calm refreshing sleep, akin to natural slumber, without any after-effects or cardiac depression. It resembles alcohol in its effects, but is a more powerful narcotic and rarely induces excitement. It is therefore a pure **hypnotic**, but its action is more speedy, producing sleep within ten to fifteen minutes. In moderate doses, it increases the flow of urine, without deranging the digestive tract, or affecting the cardiac or respiratory

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centres, which are paralysed only by enormous doses, death taking place from respiratory failure. It is partly eliminated by the breath, to which it imparts an unpleasant ethereal odour. A roseolous rash is sometimes noticed on the skin.

Poisoning from paraldehyde is rare. Two fatal cases have recently been recorded. In one a dose of 6 drs. proved fatal, in another a total quantity of 2 oz. taken during 36 hours proved fatal. Post mortem examination showed gastric mucosa hardened, wrinkled and greyish-white resembling the condition found in phenol or corrosive sublimate poisoning. *(B.M.J. Epitome, May 18, 1929).*

Therapeutics

Paraldehyde may be safely used as a hypnotic in **insomnia of cardiac** or **respiratory diseases, mania, hysterical excitement,** etc. It has been tried in asylum practice and is considered to be a valuable remedy. It is used chiefly where chloral is contra-indicated, and is valuable in **delirium tremens.** Constant use may produce toleration of the drug.

Its action is short-lived and is useless in cases where prolonged sleep rather than speedy induction is required. A paraldehyde habit though known is of rare occurrence. Its only defect is the disagreeable taste and odour and that sometimes its use is followed by excitement and delirium.

Since it is absorbed when given by the rectum, its use has been advocated as a **basal narcotic** preliminary to administration of some volatile anæsthetic. It is used per rectum dissolved either in oil or saline solution. Its action in saline is both quicker and surer than when given in oil, but its relative insolubility in the former makes the bulk of the fluid to be introduced rather large. The usual dose is 1 dr. for every stone of body weight. The solution used is paraldehyde 1 dr., normal saline $1\frac{1}{4}$ oz., glucose 5 p.c. It is a safe drug and is free from undesirable after-effects. The patient falls asleep within 30 minutes. It is also used by the same route as a **sedative** in mania, eclampsia, tetanus and other convulsive diseases.

It has also been used combined with ether intravenously as a **general anæsthetic** for short operations, $1\frac{1}{2}$ to 4 drs with an equal amount of ether in 5 oz. of normal saline.

Two ounces given per rectum proved fatal.

Prescribing hints.—Its pungent disagreeable taste may be disguised by mixing it with syrup and tincture of orange or giving it in almond mixture, in syrup and peppermint water, or in capsules. Large doses should be emulsified with compound tragacanth powder. Remember that you order sufficient water to dissolve all the paraldehyde, and that a small dose repeated within an hour is better than a single large dose.

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TRIBROMETHYL ALCOHOL

(Not Official)

Syn.—Avertin

Source.—In white crystalline powder. Contains 80 p.c. of bromine which intensifies its narcotic action. Soluble in 3 parts of water. It is dissolved in amylene hydrate (2 in 1), and 1 c.c. solution contains 1 grm. This is supplied as 'avertin liquid.'

Dose.—0.06 to 0.12 grm. per kilo of body weight. Administered per rectum mixed with water (2½ p.c. solution) half an hour before commencing the operation after the rectum has been washed out the previous evening and again three hours before operation.

Action and Uses

Avertin is rapidly absorbed and induces **anæsthesia** within 10 to 20 minutes and the patient returns to consciousness in 60 to 90 minutes after injection. It is rapidly eliminated by the urine.

It causes a **fall of blood-pressure** by depressing the heart and the vaso-motor system, it **depresses the respiratory centre** which becomes less sensitive to CO_2, and death follows from respiratory paralysis. This is counteracted by injection of **Coramine.**

At first avertin was used to induce general anæsthesia, but unfortunately a dose sufficient to induce anæsthesia was found unsafe and caused death from respiratory failure. Therefore it is used in smaller safe doses as a **basal narcotic** *per rectum* supplemented by light administration of ether or some local anæsthetic.

For rectal use the dose is 0.1 to 0.15 grm. per kilo of body weight and is administered diluted with 40 times distilled water and slowly thrown up the rectum. If an injection of hyoscine is given the patient falls asleep by the time rectal instillation is completed, when he can be removed for operation. The anæsthesia should be supplemented by ether administered by open method.

It is soon detoxicated by the liver where it combines with glycuronic acid to form urobromic acid, in which form it is excreted by the urine. Consciousness returns within a few minutes after the administration has been completed.

It is as a rule a relatively safe anæsthetic and free from post-operative complications. It however causes some toxic changes in the liver and fatal cases of acute yellow atrophy of the liver, resembling delayed chloroform poisoning, have been described in animals after avertin. Since it increases the risk of toxic changes in the liver in chloroform anæsthesia the two drugs should not be used at the same time.

There is evidence that avertin and thyroxin are in some way antagonistic to each other, and patients suffering from toxic goitre with high basal metabolic rates feel the greatest benefit of the drug.

Contra-indications.—(1) Patients with low basal metabolic rates; they do not eliminate the drug freely; (2) abnormally low blood pressure; (3) when other drugs are used which lower blood pressure or depress the respiration, *e.g.*, chloroform or morphine; (4) in operations near the rectum or anus; (5) any toxic condition; and (6) diseases of the liver and in nephritis.

Note.—Avertin is an unstable compound and should be tested before use by a few drops of 1 in 1000 solution of congo red, if no change of colour takes place then it is safe.

Amylene Hydrate. *Syn.—Tertiary Amyl Alcohol.*—It is *Dimethyl ethyl Carbinol.* As a *hypnotic* it stands midway between paraldehyde and chloral, and is stronger than the former but weaker than the latter. In small doses it stimulates the central nervous system which is depressed in large doses, and causes a fall of temperature. It is used with avertin to counteract the depressant effect of the latter drug when used as a basal narcotic. *Dose.*—30 to 60 ms. or 2 to 4 mil.

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(*d*) Sulphonal Group

These drugs owe their properties to the presence of Alkyl radicals (methyl, ethyl, etc.). It has been found that the introduction of the radical ethyl C_2H_5 into an organic compound frequently confers upon it a sedative action and these become more powerful hypnotics.

SULPHONAL

Sulphonal. $C_7H_{16}S_2O_4$

Syn.—Sulphonmethane, U.S.P.

Source.—It is *diethylsulphonedimethylmethane*, and obtained by the oxidation of the product of the interaction of ethyl mercaptan and acetone.

Characters.—Colourless, prismatic crystals, or a white powder; odourless; nearly tasteless. *Soluble* in 450 parts of water, in 15 parts of boiling water; in 80 parts of alcohol (90 p.c.).

B.P. Dose.—5 to 20 grs. or 0·3 to 1·2 grms.

METHYLSULPHONAL

Methylsulphonal. $C_8H_{18}S_2O_4$

Syn.—Sulphonethylmethane, U.S.P.; Diethyl-sulphone-ethyl-methyl methane. "Trional."

Source.—Obtained by the oxidation of the product of the interaction of methyl ethyl ketone and ethyl mercaptan.

Characters.—Colourless, lustrous scales, or a white powder; odourless; taste, slightly bitter. *Soluble* in 320 parts of water; in 12 parts of alcohol (90 p.c.).

B.P. Dose.—5 to 20 grs. or 0·3 to 1·2 grms.

ETHYLSULPHONAL

(*Not official*)

Syn.—"Tetronal." Diethyl-methane-diethylsulphone.

Source.—Sulphonal, in which two of the methyl groups have been replaced by two of ethyl.

Characters.—Shining white, crystalline tablets, or acicular crystals with no smell but a camphoraceous bitter taste. *Solubility.*—1 in 550 of water, 1 in 12 of alcohol.

Dose.—10 to 20 grs. or 0·6 to 1·2 G.

Pharmacology and Therapeutics of Sulphonal and Methylsulphonal

Sulphonal is a powerful **hypnotic** and does not depress the heart or cause the disagreeable after-effects of opium. It has no analgesic property and acts by virtue of its solubility in lipoids. It takes about four to five hours to produce sleep as its absorption is slow and uncertain. It is very useful in simple insomnia, and may safely be given in heart disease. On the other hand, it is powerless when sleeplessness is due to pain and cannot produce that soothing effect on the brain which is induced by morphine.

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It is excreted slowly and may have a cumulative effect, and its prolonged administration is sometimes followed by *hæmatoporphyrinuria*, which makes the urine cherry-red. This is more common with anæmic women and is accompained by pain in the stomach, vomiting, weakness and ataxia, confusion, partial paralysis, suppression of urine, collapse and death. These symptoms appear several days after administration of the drug and may be after one or two weeks. It rarely leads to the sulphonal habit. It is decomposed in the body and is found in the urine as ethyl sulphonic acid.

It has yielded good results in **chorea**, in **trismus neonatorum** and in **diabetes**; and it relieves spasms and cramps in fractured limbs.

Although enormous doses have been taken without any ill results, its administration is not without risk when given to patients in a state of physical prostration, and alarming symptoms have occurred after 20 gr. doses given to patients convalescent from influenza. *Restlessness, palpitation, giddiness*, and *confusion of thoughts* have occasionally been observed to take the place of sleep, specially in those suffering from chronic constipation.

Trional resembles sulphonal in its effects, but it is more prompt, inducing sleep in from 30 to 60 minutes. It is slightly cumulative, the toxicity appearing to increase in proportion to the increase in the ethyl groups. It has been largely used in **mental diseases** in which sulphonal has little or no effect. Tetronal is rarely used now.

Prescribing hints.—Sulphonal may be given either in cachets or suspended in mucilage, but the best method of administration is to dissolve it in two-thirds of a tumblerful of *boiling* water, or hot soup or milk and then stir until it is cool enough to drink. It should be taken at least four hours before bedtime. When given in cachets it may remain undissolved in the stomach for hours, giving the patient no relief at night, and making him feel sleepy all the following day.

(*e*) Urea Derivatives

BARBITONUM

Barbitone. Diethyl-barbituric Acid. $C_8H_{12}N_2O_3$

Syn.—Malonurea; "Veronal"; Diethyl-malonyl-urea; Barbital.

Source.—It is 5 : 5-diethylbarbituric acid, obtained by the condensation of ethyl diethylmalonate with urea.

Characters.—A white, crystalline powder. Inodorous; taste, faintly bitter. *Solubility.*—In about 170 parts of water, more soluble in hot water, and in alcohol (90 p.c.).

B.P. Dose.—5 to 10 grs. or 0·3 to 0·6 grm.

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BARBITONUM SOLUBILE

Soluble Barbitone

Syn.—Soluble Barbital; "Medinal"; Veronal Sodium.

Source.—Obtained by the interaction of barbitone and sodium hydroxide. Contains not less than 97 p.c. of $C_8H_{11}O_3N_2Na$.

Characters.—A white, crystalline powder; odourless; taste, bitter *Soluble* in 6 parts of water; slightly in alcohol (90 p.c.); insoluble in ether and in chloroform.

B.P. Dose.—5 to 10 grs. or 0·3 to 0·6 grm.

CARBROMALUM

Carbromal

Syn.—"Adalin"; Uradal.

Source.—Prepared by the action of *a*-bromo-*a*-ethylbutyrylbromide on urea.

Characters.—A white, crystalline powder; almost odourless and tasteless. *Soluble* in 3000 parts of water, in 18 parts of alcohol (95 p.c.), in 14 parts of ether, and in 3 parts of chloroform.

B.P. Dose.—5 to 15 grs. or 0·3 to 1 grm.

PHENOBARBITONUM

Phenobarbitone

Syn.—Phenobarbital; "Luminal"; "Gardenal."

Source.—Obtained by the condensation of ethyl phenyl-ethylmalonate with urea.

Characters.—A white, crystalline powder; odourless; taste, slightly bitter. *Soluble* in 1000 parts of water, in alcohol (90 p.c.), in ether, in chloroform, and in solutions of alkali carbonates and hydroxide.

B.P. Dose.—$\frac{1}{2}$ to 2 grs. or 0·03 to 0·12 grm.

PHENOBARBITONUM SOLUBILE

Soluble Phenobarbitone

Syn.—Soluble Phenobarbital: Luminal-Sodium.

Source.—Obtained by the interaction of phenobarbitone and sodium hydroxide.

Characters.—A white, hygroscopic powder; odourless; taste, bitter. Very *soluble* in water, soluble in alcohol (90 p.c.). Insoluble in ether.

B.P. Dose.—$\frac{1}{2}$ to 2 grs. or 0·03 to 0·12 grm.

Non-official Preparations

1. **Nirvanol.**—*Phenyl-ethyl-hydantoin.*—A tasteless crystalline powder. Sightly soluble in water. *Hypnotic* and *sedative.* Useful in *chorea.* Daily dose for a child 9 to 14 years is 5 grs. or 0·3 G. Treatment is followed, after one to two weeks, by pyrexia and a morbilliform rash, known as "nirvanol sickness" when the treatment should be stopped. There is œdema of the eye lids, conjunctivitis and true eosinophilia. *Dose.*—2½ to 7 grs. or 0·15 to 0·45 grm.

2. **Proponal.**—*Dipropyl-Barbituric Acid.*—A homologue of veronal; white crystalline powder. Very narrow margin between therapeutic and toxic dose. Some consider it more toxic than veronal. *Dose.*—2 to 8 grs. or 0·12 to 0·5 G.

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3. **Bromural.** *Syn.—Uvaleral; Dormigene.*—Colourless crystals. Soluble in hot water, ether, alcohol, and the alkalies. Contains 36 p.c. bromine. *Hypnotic* in *neurasthenia.* Sleep within 5 to 25 minutes. *Dose.*—5 to 10 grs. or 0·3 to 0·6 G.

4. **Pentobarbital Sodium.** *Syn.*—"*Nembutal.*"—A white, crystalline powder, freely soluble in water with a slightly bitter taste. *Dose.*—½ to 3 grs. or 0·03 to 0·2 grms. *per os,* or per rectum. As *basal narcotic.* 3 to 5 grs. or 0·2 to 0·3 grm. in 10 c.c. of water, intravenously.

5. **Amytal.**—*Iso-amyl-ethyl-barbituric acid.*—A white, crystalline powder, with slightly bitter taste. Soluble in alcohol and ether, slightly in water. *Dose.*—As a *sedative,* ¼ to ¾ gr. *(per os);* as a *hypnotic,* 2 to 5 grs.; as *general anæsthetic,* 3 to 10 grs.

6. **Phanodorm.** *Syn.—Cyclo-hexenylethyl Barbituric Acid.*—A white, crystalline powder, with a bitter taste. *Dose.*—3 grs. in tablets; in mild insomnia, 1½ grs.

7. **Theominal.**—A combination of theobromine 0·3 G., and luminal 0·03 G. In *arteriosclerosis, angina pectoris,* and other heart affections, and climacteric disorders. *Dose.*—5 grs. in tablets.

8. **Dial.** *Syn.—Diallyl barbituric acid.*—A homologue of barbituric acid. *Dose.*—1½ to 5 grs. or 0·1 to 0·3 grm.

9. **Evipan.**—Methyl-cyclo-hexenyl-methyl barbiturate. A white crystalline powder, sparingly soluble in water, more freely in hot alcohol. A hypnotic. *Dose.*—4 to 6 gr. or 0.25 to 0.4 grm.

10. **Evipan Sodium.**—Sodium salt of evipan. Freely soluble in water. In ampoules containing 1 grm. of the powder. *Dose.*—5 to 15 grs. or 0.3 to 1 gm.

Pharmacology of Barbiturates

The derivatives of this group have practically the same action, *viz.* **sedative** and **hypnotic,** but differ only in degree and duration, and this depends partly upon the rate of excretion and partly upon the rate of destruction of the drug. Since barbituric acid is unstable and does not possess any narcotic action these drugs are rendered useless by the oxidation of their side-chains, and the compounds with unstable side-chains produce very short action. They all belong to the *aliphatic series,* and as such their action varies with their solubility in fats. The intensity of their action can be modified with the amount used, and will produce sleep, complete insensibility or coma according to the dose. They are **analgesics,** but in this effect they are inferior to the drugs of the antipyretic group. Barbitone is a sedative and hypnotic; phenobarbitone, amytal and pernocton are more analgesic and less hypnotic, depress the motor area, and are slightly more toxic.

Barbitone and soluble barbitone (medinal) produce refreshing sleep without any unpleasant after-effects. They take about half an hour or more to produce sleep by their effects entirely on the central nervous system. They are about twice as active as chloral and four times as strong as sulphonal.

As a rule no untoward effects are observed either on respiration or circulation in full doses required to produce complete anæsthesia. Sometimes sleep is preceded by excitement and delirium.

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Respiration and circulation.—No effect is observed on respiration, except some slowing, which is not more than found in natural sleep. Toxic doses depress the centre, when breathing becomes slower, shallower and even irregular. Death takes place from pulmonary œdema and paralysis of the centre.

Ordinary hypnotic doses have no effect on circulation. The blood-pressure remains normal though the heart may be a little quickened. Given intravenously, as for the production of anæsthesia, the pressure falls but returns to normal soon.

Temperature.—Sedative doses lower the temperature slightly, which becomes very low in coma due to depression of the medullary centres and also from lessened movements.

Smooth muscles.—All depress the smooth muscles producing loss of tone specially of the uterus. Amytal however has very little effect on the normal uterine contractions, and in anæsthesia produced by amytal the uterine contractions continue.

Margin of safety.—Since these drugs are extensively used as hypnotics and analgesics it is necessary that the margin of safety between the hypnotic dose and the lethal one represented by the ratio $\frac{\text{minimum lethal dose}}{\text{minimum therapeutic dose}}$ should be known. The higher this figure the safer the drug. Luminal is 1.3; barbitone 1.6; soneryl, nembutal and phanodorm, 2.4; dial 2.5; evipan, 5. Thus it is not very safe to give luminal in full hypnotic doses, although in sedative anti-epileptic dosage it is free from immediate risk.

Excretion.—Barbitone passes out of the body in most part unchanged, about 70 p.c. being found in the urine, and takes several days to eliminate even after a single dose. Its use should not therefore be continued for more than one week, otherwise symptoms of poisoning may develop. 65 p.c. of pernocton, 30 p.c. of dial, between 10 and 40 p.c. of luminal, and no amytal could be recovered from the urine. Evipan is said to be metabolised completely in a few hours. Traces have been found in the cerebro-spinal fluid and milk.

Toxicology.—The action of these derivatives varies in different individuals. While symptoms of poisoning have been reported with 1 gr. of veronal, recovery has also taken place even after 1 dr. All these drugs are more or less cumulative and the symptoms of over-dosage are often due to this factor, *i.e.*, when continued for long even in therapeutic doses, but is specially common when excretion is also scanty due to the kidneys not functioning properly. A case of delusional insanity following nembutal-ether anæsthesia has been recorded after 3 grs. (two capsules) of nembutal with $\frac{1}{100}$ gr. of atropine by the mouth before administration of gas-ether anæsthesia *(Royal Society of Medicine, Aug.* 1932). A case of acute veronal poisoning has been recorded following taking of 24 grms. in a single dose. Profound coma, profuse perspiration, cyanosis and imperceptible pulse were observed even on the fourth day. There were incontinence of urine and fæces,

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loss of tendon and corneal reflexes, dulling of general sensibility, mydriasis and profuse secretion of saliva. If recovery takes place there is diplopia and ptosis. No albumin or traces of veronal was detected in the urine.

Treatment of Veronal Poisoning.—If seen within four hours, repeated washing of the stomach with warm water. Put 1 pt. of strong hot coffee with some milk and 1 oz. of castor oil. If seen after six hours, lavage is still useful. Strychnine $\frac{1}{30}$ gr. and atropine $\frac{1}{100}$ gr. every four hours. Subcutaneous injection of warm saline solution and rectal use of saline and glucose 4 p.c. Oxygen if cyanosis is present. Hasten removal of the poison from the central nervous system specially the vital medullary centres by lumbar puncture.

THERAPEUTICS OF BARBITURATES

The chief uses of the different preparations of this group are as hypnotics, sedatives, analgesics and anæsthetics.

As *hypnotics* these derivatives have come to the forefront and are used in preference to the sulphonal group because of their liability to poisonous effects and paraldehyde which is disagreeable. They produce almost natural sleep within 20 to 30 minutes lasting for 6 to 8 hours from which the patient wakes up refreshed, although some lassitude remains during the day. They can be used in any form of insomnia and are of extreme value when sleeplessness is due to **nervous excitability, mental disease** and **cerebral excitement.** As hypnotics, veronal and medinal are given in $7\frac{1}{2}$ gr., and luminal and amytal in $1\frac{1}{2}$ gr. doses. Luminal sodium can also be given hypodermically in 20 p.c. solution.

They are valuable *sedatives* to the brain and as such are more prompt than bromides and can be used in all cases where bromides are indicated. Of all the preparations luminal is largely used. It is also useful in **vomiting of pregnancy** and **sea-sickness** in doses of 0.06 to 0.12 grm. (1 to 2 grs.) half an hour before meals. Alone or combined with belladonna it is useful in **pyloric stenosis** and **colic.** They are all used to **reduce convulsion** in mania, delirium tremens, excitement following withdrawal of morphine, epilepsy, strychnine poisoning and tetanus, although luminal, and sodium amytal are preferred. In **epilepsy** luminal is more valuable in acute attacks and reduces both the number and severity of the fits, and does not produce that mental hebetude so common after prolonged use of bromides. The best method of administration is to prescribe $1\frac{1}{2}$ to 2 grs. twice a day, or in nocturnal attacks only one dose just before going to bed. The dose requires to be regulated, keeping in mind the idiosyncrasy of the patient and the liability of the drug to produce skin rash. It is not a cure for epilepsy and requires to be continued for a long time, possibly for years, and the dose gradually reduced. If no change is produced at the end of six months the treatment should be stopped.

As *analgesics* they are useful in headaches of all kinds,

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and are valuable in reducing pains of a neuralgic nature, *e.g.*, **sciatica, intercostal neuralgia, lumbago, dysmenorrhœa**, etc. They are often used in combination with amidopyrine derivatives, *e.g.* Allonal and Veramon.

As *anœsthetics* they have been used either for the production of general anæsthesia or as a preliminary to the use of volatile anæsthetics. Their use as a general anæsthetic by the production of narcosis is open to many objections. Being non-volatile they cannot be given by inhalation and therefore the dose cannot be regulated. If, for instance, a small dose has been given it can always be increased, but if a large dose has been introduced it cannot be withdrawn; whereas the dose of volatile anæsthetics can be regulated at will according to the need of the patient. Moreover owing to their slow excretion the narcotic effect lasts for many hours often with injurious effect to the patient. Their use therefore has not been generally accepted by many competent authorities inasmuch as the mortality following their use was greater than with volatile anæsthetics. Moreover the intravenous injections require large amounts of alkali for solution and when they enter the blood they are precipitated and remain as foreign bodies in a colloidal state, thus altering the colloidal equilibrium of the blood which may give rise to certain reflex effects. In fact the Council of Pharmacy and Chemistry of the American Medical Association recommend that the intravenous injection of the barbiturates should only be used in emergencies and then even when the oral administration is not possible. On the other hand for the production of **basal narcosis** as a preliminary to volatile anæsthetics they are largely used nowadays on the idea that the patient may be anæsthetised without any preliminary excitement and with a small amount of volatile anæsthetic. Unfortunately the prolonged post-operative analgesia is often accompanied by pulmonary complications resulting from prolonged respiratory depression. It is therefore necessary that preparations with short duration of action should be preferred to avoid post-operative effects which often cause anxiety. In any case it is essential when a basal narcotic is used in a combination anæsthesia, that no further narcotic of any kind should be given after operation until the patient is completely conscious and complains of pain or is very restless.

Most of the drugs selected for the purpose are those that are rapidly decomposed in the tissues of the patient, and the drug is introduced slowly by the intravenous route. There are however certain possible dangers which should be remembered, *viz.* (1) *idiosyncrasies* to the drug; (2) *inability on the part of the body to decompose the drug*, as happens in patients with bad liver; (3) *combination of several narcotics*

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e.g. morphine is specially dangerous and may depress the respiration profoundly.

The different preparations used as basal narcotics are :—

Pernocton.—Sodium beta-bromallyl-barbituric acid. This is given intravenously about quarter of an hour before starting the inhalation anæsthesia. Resembles nembutal, but it is a more powerful hypnotic. The dose is 1 c.c. of a 10 p.c. solution per 12.5 kilo of body weight. Does not produce any marked fall of blood presure like amytal. No morphine is required but atropine may be given with advantage. *Dose.*—5 grs. or 0·3 grm.

Luminal is given by the mouth on the evening before operation, 10 grs. at 9 p.m. If the patient is drowsy in the morning, half the dose is given two hours before operation.

Nembutal.—Sodium ethyl-methyl-butyl barbiturate, is more sedative than hypnotic, and is less often followed by restlessness or delirium and is safer than amytal. For production of basal narcosis it is given intravenously ten minutes before operation. The solution should be freshly prepared and must be quite clear, and the injection given with the patient in bed, or on the operation table with a solution of $7\frac{1}{2}$ grs. in 10 c.c. at the rate of 1 c.c. per minute; the dose being the minimum amount required to put the patient into a quiet sleep. *By mouth the dose* is $1\frac{1}{2}$ to 4 grs. with morphine $\frac{1}{4}$ gr. three quarters of an hour before operation.

Sodium Amytal (sodium iso-amyl-ethyl-barbiturate) is a powerful hypnotic and rapidly produces loss of consciousness and general anæsthesia. It is given intravenously in 10 p.c. solution at the rate of 1 c.c. per minute. Unconsciousness is induced very rapidly, the usual quantity required being 7 to 15 grs. It reduces the amount of ether by ten per cent. As the anæsthesia is produced very rapidly the injection is given a few minutes before operation. Owing to its effect on respiration and vaso-motor centre, it causes a great fall of blood pressure and respiratory weakness. It is however completely destroyed in the system. It is useful in strychnine poisoning when given in full doses.

Soneryl Sodium.—Sodium derivative of butylethyl-barbituric acid. A sedative and hypnotic. Administered as a pre-anæsthetic basal narcotic in doses of $2\frac{1}{4}$ grs. per 36 pounds body weight. It is closely allied to nembutal but less toxic and has the advantage of being effective when given orally an hour before operation and atropine half an hour later. The sleep after operation is not excessive, but some patients become restless which is easily controlled by morphine. Except some depression of breathing in a few instances no other complication has been recorded.

Soneryl is a sedative and hypnotic in doses $1\frac{1}{2}$ to $4\frac{1}{2}$ grs.

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Evipan Sodium.—It is extensively used as a non-volatile general anæsthetic. It is rapidly detoxicated by the liver, a portion remaining unchanged is excreted in the urine. It is administered intravenously; the amount contained in the ampoule is dissolved in 10 c.c. of sterile distilled water just before use, as it is very unstable. The injection is made into a vein, and the patient is asked to count aloud, the rate of injection is 1 c.c. in 15 seconds, and about 3 c.c. is required to produce unconsciousness. For short operations the same amount is further added and twice as much for long operation. For elderly and debilitated patients half the amount required to produce sleep should be given.

A deep yawn just before the disappearance of consciousness, twitching of the face muscles and jactation of the limbs are common. Pupils are moderately dilated and react to light. Corneal reflex is lost during complete anæsthesia. The patient regains consciousness in ten to twenty minutes, but remains drowsy and drops off to sleep again if left undisturbed.

The use of barbiturates is not always unattended with sequelæ. Sometimes the patient will sleep deeply, for a period sufficiently long to cause anxiety. A minor but troublesome complication is restlessness preceding return to full consciousness. This however is less with nembutal than with others. All basal narcotics cause depression of respiratory centre, so that in some cases the breathing becomes so quiet and shallow that the patient scarcely takes sufficient anæsthetic to secure surgical anæsthesia. Cyanosis is also another complication. Toxic condition and hyperthyroidism increase the sensitiveness to these derivatives, 6 grs. of nembutal proved fatal in Graves' disease.

URETHANE

(Not official)

Syn.—Ethyl Carbamate.

Source.—Prepared by the action of ammonia upon ethyl chloroformate.

Characters.—Colourless prismatic crystals, having a cooling saline taste; no smell. Easily soluble in water.

Dose.—1 to 2 grms. or 15 to 30 grs.

Pharmacology and Therapeutics

In *urethane* the depressing effect of ethyl on the medulla is counteracted by the stimulating effect of the carbamic radical. Thus it is free from danger to respiration and the heart even in very large doses. It is the safest of all hypnotics but less certain. It retards digestion but does not derange the stomach. At first it produces some excitement, but this is quickly followed by natural sleep, with some slowing of respiration and the pulse. Blood-pressure is not lowered, but large doses lower the temperature and weaken and even abolish the reflexes. It does not relieve pain. It must be given in full doses of 20 to 30 grs. which may be repeated in an hour or two if sleep does not follow the first dose. It is specially suitable for children, cases of delirium tremens, acute mania, and in the insomnia of heart disease. It is antagonistic to strychnine and has proved more useful than chloral in tetanus.

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Class B : Drugs acting on the Cord

The cord performs three specific functions, *viz.*—(1) the conduction (*a*) of sensory or afferent, and (*b*) of motor or efferent impressions ; (2) the reflex action ; and (3) the origination of impulses by special nerve centres, e.g. the sweat centres, located in the cord. The drugs acting on the cord may be divided into *spinal stimulants*, or those which increase the irritability of the anterior cornua and produce convulsions ; and *spinal depressants*, or which depress or paralyse the activity of the anterior cornua.

Convulsants

Drugs which stimulate the general nervous system cause exaggerated reflexes, and if the stimulation is sufficiently strong may produce convulsions, which may be *clonic* or *tonic*. Many factors contribute to the production of convulsions, *viz.* direct stimulation either of the muscles, as by veratrine ; or of efferent motor nerves, as by physostigmine ; excitation of the brain, medulla and cord either directly by a drug, or as a result of asphyxia ; or reflexly as a result of strong afferent stimulation.

Direct stimulation of the cerebrum is as a rule followed by convulsions of a different nature inasmuch as they are not produced by any sensory stimuli and have not a reflex character in the ordinary sense. They are irregular and only a limited group of muscles are involved and unlike strychnine no inhibition of the antagonist group of muscles takes place. The convulsions correspond to the normal co-ordinated combination of movements, *i.e.*, they are *clonic* or *epileptiform*. Medullary stimulation, as from camphor and picrotoxin, also produces clonic convulsions but these are more irregular and asymmetrical.

Convulsions induced by strychnine are spinal and reflex in character, and are due to some afferent stimulation, and affect all the muscles in a symmetrical way. They are *tetanic*, and other drugs which act like strychnine, but in a milder way are caffeine, ammonia, cocaine and thebaine.

NUX VOMICA

Nux Vomica

Syn.—Poison-nut. **Syn. I. V.**—*Kuchila*, Beng., Hind.

Source.—The dried ripe seeds of *Strychnos Nux-vomica*. Contains not less than 1.2 p.c. of strychnine.

Characters.—Disc-shaped, nearly flat, sometimes irregularly bent, 2 to 2.5 cm. in diameter, about 6 mm. thick; rounded or somewhat acute at the margin, where there is a small prominence from which a raised line passes to the central hilum. Surface ash-grey, covered with short satiny hairs. Endosperm large, horny. Cotyledons small, leafy. Taste, intensely bitter. No odour. The *Ignatius' Beans* are

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the seeds of *Strychnos Ignatia*, they are olive-shaped, and contain more strychnine.

Composition.—(1) *Strychnine*, 0·2 to 0.5 p.c. varying in different seeds. (2) *Brucine*, 0.5 to 1 p.c. (3) *Igasuric acid*, with which strychnine and brucine are united. (4) *Loganin* a glucoside.

Official Preparations

1. **Nux Vomica Pulverata.** *Syn.*—*Pulvis Nucis Vomicæ.*—Nux vomica reduced to a fine powder and adjusted, if necessary, either by admixture of powdered nux vomica, or powdered lactose, to contain 1.2 p.c. strychnine. 4 grs. contain $\frac{1}{20}$ gr. of strychnine. **B.P. Dose.—1 to 4 grs. or 0.06 to 0.25 grm.**

2 **Extractum Nucis Vomicæ Siccum.**—Contains 5 p.c. of strychnine, or $\frac{1}{20}$ gr. in 1 gr. **B.P. Dose.—$\frac{1}{4}$ to 1 gr. or 0.015 to 0.06 grm.**

3. **Extractum Nucis Vomicæ Liquidum.**—Contains 1.5 p.c. of strychnine, or $\frac{1}{24}$ gr. in 3 ms. **B.P. Dose.—1 to 3 ms. or 0·06 to 0·2 mil.**

4. **Tinctura Nucis Vomicæ.**—Contains 0.125 w/v of strychnine, or $\frac{1}{30}$ gr. in 30 ms. **B.P. Dose.—10 to 30 ms. or 0.6 to 2 mils.**

STRYCHNINAE HYDROCHLORIDUM

Strychnine Hydrochloride. $C_{21}H_{22}N_2O_2,HCl,2H_2O$

Source and characters.—It is the hydrochloride of the alkaloid strychnine. Small colourless, prismatic crystals. Efflorescent in the air, very bitter. *Solubility.*—1 in 40 of water.

B.P. Dose.—$\frac{1}{32}$ to $\frac{1}{8}$ gr. or 0.002 to 0.008 grm.

Official Preparations

1. **Liquor Strychninæ Hydrochloridi.**—Contains 1 p.c. w/v of strychnine hydrochloride, or $\frac{1}{9}$ gr. in 12 ms. **B.P. Dose.—3 to 12 ms. or 0.2 to 0.8 mil.**

2. **Syrupus Ferri Phosphatis cum Quinina et Strychnina.** *Syn.*—*Easton's Syrup.*—1 gr. of ferrous phosphate, or $\frac{1}{2}$ gr. of iron, $\frac{1}{60}$ gr. strychnine hydrochlor. and $\frac{4}{5}$ gr. of quinine hydrochlor. in 60 ms. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Non-official Preparations

1. **Strychninæ Arsenas.**—Small, white acicular crystals soluble 1 in 14 of water. *Dose.*—$\frac{1}{64}$ to $\frac{1}{16}$ gr. or 0.001 to 0.004 G.

2. **Strychninæ Phosphas Acidus.**—Shining acicular crystals. Soluble 1 in 31.5 of water. *Dose.*—$\frac{1}{64}$ to $\frac{1}{16}$ gr. or 0·001 to 0·004 G.

3. **Strychninæ Sulphas, U.S.P.**—Prismatic, white or colourless crystals. Soluble 1 in 35 of water. *Dose, U.S.P.*—0.002 grm. or $\frac{1}{30}$ gr.

4. **Strychninæ Nitras, U.S.P.**—In colourless, glistening needles, or as a white crystalline powder. *Dose, U.S.P.*—0.002 grm. or $\frac{1}{30}$ gr.

Pharmacology

Externally.—Strychnine is a powerful antiseptic while brucine is a local anæsthetic.

Internally. **Gastro-intestinal tract.**—Being intensely bitter both nux vomica and strychnine are typical **stomachics and tonics**, increasing the secretion of gastric juice, and thereby sharpening appetite and promoting digestion like gentian, calumba, etc., but more powerfully. They **increase the peristaltic movements of the intestines** by augmenting the reflex excitability of Auerbach's plexus and may thus act

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as a purgative. The preparations of the crude drug being less easily absorbed, remain for a longer time in the intestine and act better than the alkaloid.

Blood.—Strychnine enters the blood from the mucous membrane or when given hypodermically. It is not known what effect it has on the living blood-corpuscles, though blood mixed with strychnine and shaken with air contains more oxygen and less carbonic acid.

Heart and circulation.—The heart is not affected in therapeutic doses, there may be some slowing of the pulse from stimulation of the vagus centre and a rise of blood-pressure from stimulation of the vaso-constrictor centres in the medulla and cord. These effects were attributed to convulsions and asphyxia, but since they occur even after abolition of convulsions by curare and exclusion of asphyxia by artificial respiration, they must be strychnine effects, although these factors may be contributory. The vessels of the splanchnic area are constricted, while those of the heart, lungs and central nervous system dilate. The general effect therefore is to raise the arterial pressure and allow more blood to flow through those organs necessary for the maintenance of the vital processes. This redistribution of the blood recuperates the heart by improving coronary circulation thereby supplying more oxygen and nutrition. The vessels of the skin also dilate. It stimulates the secretion of adrenaline and thus may produce indirectly circulatory effects.

Respiration.—The medullary and spinal respiratory centres are stimulated rendering the respiration deeper and quicker. The latter becomes so active that if the cord of an animal is cut below the medulla, respiration is not entirely stopped; again if the drug is given after the section of the cord, respiration returns. The effect is more marked when the centre is depressed by some narcotics. The respiratory muscles participate in the general tetanus and the patient dies asphyxiated from rigidity of the thoracic muscles and diaphragm.

In therapeutic doses the bronchial muscles are improved in tone, and although this may make it useful in relaxed conditions of the bronchus it will be harmful in spasmodic state of the bronchi, as in asthma. The cough centre is also stimulated.

Brain.—The higher centres are stimulated though feebly even in toxic doses and the mind remains clear to the last, and the patient feels the excruciating pain of convulsions. Small doses render the special senses more acute. Thus it strengthens the mental power and sharpens the senses of sight, smell and hearing, and pain is more keenly felt. It increases the field of vision and makes the eye more sensitive to slight differences in light, due to its effects on the retinal cells and not to changes in the brain.

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Medulla and cord.—Strychnine **stimulates** the **respiratory** and the **vaso-motor** centres in the medulla. But its main action is on the cord. In moderate doses it **increases the tone of the muscles,** *i.e.*, produces exaggerated reflexes, and makes the cord hypersensitive, so that a slight stimulus, which ordinarily causes no marked response, is followed by increased reflex excitability. In poisoning, a slight peripheral stimulus, like the prick of a pin or a flash of lightning or a sound, will provoke convulsions, which are sudden in onset and involve all the voluntary muscles of the body. They are at the beginning intermittent, but subsequently become tetanic, and although appear to be spontaneous are in reality always elicited by some external stimulus. The cause of these convulsions has been the subject of much controversy. That they are not cerebral is shown by the fact that they can be produced in a decapitated animal. Moreover, if the posterior nerve roots are divided, or if the entire surface of the skin is anæsthetised by cocaine so that no afferent impulse can reach the spinal cord, no convulsion follows. If, however, the central ends of the cut nerves are stimulated, convulsions can be obtained. The convulsions therefore have their origin in the cord, though not initiated there inasmuch as they are reflex, being the result of afferent impulses to external stimuli. Ordinarily when a stimulus is applied, as elicited by an ordinary simple reflex, it will not only cause contraction of one group of muscles, but by co-ordination will cause relaxation of the corresponding antagonist group of muscles (Sherrington). Thus there are two components working, one the motor and the other inhibitor. The stimulation of the flexor muscles, will lead to inhibition of its antagonist the extensor muscles, and both cannot be put into action simultaneously unless the stimulus is abnormally strong. After a toxic dose of strychnine the contraction is not limited to the usual group but also to the opposing group of muscles, *i.e.*, the flexors and extensors contract simultaneously. Strychnine therefore causes a breakdown of the normal inhibitory influence and causes contraction of all the groups of muscles, and of the two sets of opposing muscles, the effect of the strongest set predominates. Therefore in case of poisoning the body becomes arched backwards, and owing to the involvement of the diaphragm and the muscles of the chest and abdomen, the respiration becomes affected.

Nerves and muscles.—Strychnine augments the capacity for muscular work and delays onset of fatigue. It has no effect on the voluntary muscles although their tone is improved through the cord. In toxic doses the functional activity of the motor nerves is depressed towards the end. This is not due to the exhaustion of the nerve tissue as has been supposed, but to the direct action of the drug on the nerves themselves.

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Metabolism.—The increased movements of the body naturally excite oxidation, and the absorption of oxygen and excretion of CO_2 are correspondingly increased. Owing to increased flow of blood through the skin there is a rise in the skin temperature, but there is more heat dissipation, and any rise of temperature from increased metabolism is counteracted, and the net result is rather a fall of temperature. Glycogen in the liver and of the muscles is considerably reduced during the spasm and may disappear entirely if the spasms be of some duration. Sugar is also passed in the urine of animals experimented upon. This at one time was supposed to be a specific action, but has been proved to be due to partial asphyxia.

Genital organs.—In moderate doses, it produces sexual desire, it is therefore an **aphrodisiac.**

Absorption and elimination.—Strychnine is rapidly absorbed mainly from the intestine. It is excreted chiefly in the urine (10 to 20 p.c.). The excretion begins within a few hours and continues usually for forty-eight to seventy-two hours, though traces may be found even after five days. Part of the alkaloid is taken up by the liver where it undergoes oxidation.

Toleration.—Some persons are more tolerant than others. Some people of India are in the habit of taking nux vomica morning and evening with *pan*; commencing with $\frac{1}{4}$ gr. they sometimes increase it to about 20 grs. (an entire nut).

Acute toxic action.—Within $\frac{1}{2}$ to 1 hour after a large and poisonous dose, the symptoms of poisoning commence. General uneasiness and soreness of the limbs, instantly followed by shooting pains in the back and then down the arms and legs, are first observed. Tetanic convulsions of the muscles soon set in, lasting for $\frac{1}{2}$ to 1 minute, when they relax, leaving the patient sweating and exhausted. They come on again and again, and the intermission gets shorter and shorter as the severity of the symptoms increases. The muscles of the jaw are only affected before death, not in the beginning. In short, the symptoms of poisoning closely resemble those of tetanus, from which they differ in (1) their rapid development; (2) want of a history of a wound, operation, etc., as in tetanus; (3) complete relaxation between the spasms in strychnine poisoning, whereas in tetanus the muscles of the back and jaw remain rigid between the spasms; (4) trismus or "lock-jaw" only appears as a late symptom, whereas it is the first symptom in tetanus; (5) death taking place soon, or the symptoms rapidly declining. Half a grain is the smallest dose that has been known to prove fatal.

Antidotes.—Pump before convulsions, or under chloroform after convulsions. Apomorphine $\frac{1}{10}$ to $\frac{1}{6}$ gr. subcutaneously, or emetics; charcoal or tannin in large quantities, potassium bromide (2 drs. to 2 ozs.) with chloral hydrate (30 to 60 grs.) repeated if necessary, or urethane and paraldehyde, morphine, alcohol in poisonous doses; chloroform inhalation, artificial respiration, etc.

Wheelcock (*Journ. Amer. Med. Assoc.* Nov. 26th 1932) records a case of recovery from strychnine poisoning by the intravenous injection of phenobarbital sodium 5 grs. followed by 15 grs. of sodium amytal dissolved in 10 c.c. of water, 1 c.c. being given per minute.

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Methyl and Ethyl compounds of Strychnine and Brucine.—Remarkable results have been obtained by Fraser and Crum Brown when strychnine and brucine were combined with methyl and ethyl radicals. These new compounds lose their convulsant action, which they ordinarily possess when uncombined, and produce general paralysis of the body by acting on the ends of the motor nerves like curare. In poisoning by any of these compounds, the heart continues to beat normally for a long time, and the muscles of the body remain for hours flaccid and contractile. Hence ethyl and methyl compounds of strychnine and brucine may be injected in strychnine poisoning as antidotes.

THERAPEUTICS

Internally. **Gastro-intestinal tract.**—Nux vomica and strychnine are largely used to promote appetite and digestion in **atonic dyspepsia,** and **weakness of digestion** during convalescence from acute illness. Tr. nucis vomicæ or liqr. strychninæ hyd. and infusion of calumba or infusion of gentian make a very efficient prescription for such cases. The following combination is largely used: ℞ Acid. hydrochlor. dil. ms. 10; tr. nucis vom. ms. 10; spt. chloroformi ms. 15; inf. gentianæ co. ad oz. 1. t. d. s. Strychnine has given satisfactory results in acute and chronic **gastric catarrh** and **gastralgia** ($\frac{1}{100}$ gr. hypodermically). Because it increases peristalsis, nux vomica is frequently given as an adjunct to purgatives. Sometimes it corrects constipation without the aid of other remedies.

Heart and circulation.—As a circulatory stimulant its value is doubted by many. Its chief use is in cases of pure failure of circulation due to vascular paralysis leading to collapse when it acts by constricting the splanchnic vessels thus sending more blood to the skin, extremities, heart, lungs and the nervous system, so that by redistribution it sends more blood to the vital organs and improves circulation and averts threatening collapse. It has no effect when the circulatory failure is purely cardiac. If however the vascular failure is a capillary stasis, or if the vessel walls have lost their excitability, stimulation of the vaso-motor centre with strychnine can be of no benefit. To get any improvement the dose should be $\frac{1}{10}$ to $\frac{1}{8}$ gr. hypodermically (Gunn).

Respiration.—As it stimulates the cough centre, it helps expectoration by provoking coughing, and is useful in chronic bronchitis, protracted pneumonia, etc., when given with other expectorants. It averts death in chloroform poisoning ($\frac{1}{30}$ gr. hypodermically). As a respiratory stimulant it is valuable in **narcotic poisoning,** *e.g.*, opium, chloral, etc., and in exhaustion of the centre, as in **pneumonia.** In these conditions improved respiration will result in increased supply of oxygen to the heart and central nervous system, and there will be a break in the vicious circle, thus enabling the patient to maintain the effect even after the stoppage

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of the drug. In these cases it should be given in full doses when it may tide over a critical period.

Nervous system.—As a spinal stimulant strychnine is used in diseases of the nervous system, but the conditions in which it can be of service are very limited, and its use requires careful discrimination. It is useful in (*a*) *paresis* or incomplete paralysis ; (*b*) *local paralysis* as that of the forearm, larynx, sphincter, etc., due to any toxic agent, as lead, alcohol, or tobacco ; (*c*) *diphtheritic paralysis* ; and (*d*) *post-operative paralysis* of stomach or intestine. Its use has been suggested in infantile paralysis, but since there is destruction of the anterior cells of the cord, the use of strychnine can have no influence in restoring the destroyed nerve cells. Indeed if used early it may be positively harmful by irritating the surrounding area of inflammation. Similarly its use in lesions of the motor area of the brain, or of the motor tract of the brain and cord can only be harmful. It should not be used (*a*) when the paralysis is of recent origin ; (*b*) when rigidity of muscles still exists ; (*c*) when there is much wasting of muscles (sometimes progressive muscular atrophy is stayed in its progress by the hypodermic injection of $\frac{1}{60}$ gr. increasing to $\frac{1}{40}$ gr. given once daily) ; (*d*) when head symptoms are present ; and (*e*) when the muscles do not respond to electricity.

Besides the above, nux vomica or strychnine can be successfully employed in atonic conditions of the bladder and sexual debility. In mental depression from overwork it should be used after the suspension of work.

Prescribing hints.—The effect of strychnine depends upon its rapidity of absorption. Given hypodermically it is two to eight times stronger than when given by the mouth. When administered per rectum the effects approach more closely the hypodermic method. Children are comparatively insusceptible to it. Toleration is not induced, on the other hand, long continued use renders the nervous system more sensitive to it.

Class C : Drugs acting on the Sympathetic and Parasympathetic Systems

The voluntary muscles are under the direct control of the central nervous system, but the activity of the involuntary muscles and of the glands is regulated by a more complex arrangement. A characteristic feature of these involuntary active organs is that they can work independently of the central nervous system and for this reason their nervous system is known as *autonomic system*, although this is also influenced in all its parts by the centres. The nerves supplying them do not pass directly from the central nervous system, but medullated fibres are projected

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from the cord and run to ganglion cells whence non-medullated fibres pass down to the different tissues. The autonomous system has been classified into (1) *cranial autonomic*; (2) *sympathetic proper*; and (3) *sacral autonomic*. The cranial and sacral autonomic systems have complementary physiological functions and are known as *para-sympathetic system*.

The *sympathetic system proper* consists of a chain of ganglia or collections of nerve cells situated on each side of the vertebral column. The "outflows" from the sympathetic arise from the dorsal and down to the fourth and fifth lumbar nerves as minute medullated fibres. These have their cell stations in the ganglia of the sympathetic cord, and in the cardiac, solar and hypogastric plexuses.

The "outflows" from the *parasympathetic* include the cranio-bulbar and the sacral outflows. The cranial group is formed by the third, the seventh, the ninth and the tenth; while the sacral group by the second, the third and the fourth sacral nerves. The parasympathetic fibres which run into the oculo-motor arise from the mid-brain and supply the ciliary muscle and the iris. The seventh and the ninth emerge from mid-brain and supply the vaso-dilators and the secreting glands in the nose, the mouth and the pharynx. The chorda tympani becomes bound up with the branches of the 5th and is distributed with them. Finally from the mid-brain emerge the vagi which supply the heart, the bronchial muscles, the œsophagus, the stomach and the small intestine, and also regulate the secretory mechanism. The fibres from the sacral region supply the vaso-dilators, the external generative organs, the bladder, the rectum, the anus, and motor fibres to the musculature of the descending colon and rectum. It will be seen that the autonomic fibres arise only from certain sections and not in an unbroken succession from the central organs, and act as conducting paths to carry impulses from the central nervous system to the different internal organs, and by means of their endings either augment or depress their functions. All the functions of these organs are performed even if the organs concerned are separated from the control of the central nervous system. The brain however influences their activity, and even psychical stimulation, *e.g.* fright, excitement or emotion, is followed by changes in the activity of the heart (acceleration), vessels (flushing), and even of different secretions (sweat).

The sympathetic and the parasympathetic systems are antagonistic to each other both physiologically and frequently pharmacologically. In most organs where the two types of nerve influences act, they affect their functions in opposite directions, *i.e.*, they lead to opposite results. Thus the pupil is contracted by the parasympathetic fibres

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running along the third nerve, while it is dilated by the sympathetic supplying the dilator pupillæ. Similarly, the parasympathetic vagus inhibits the heart, while the sympathetic accelerates it. It must not be supposed that the sympathetic alone is concerned with augmentation and the parasympathetic with inhibition. Though the vagus is the inhibitor nerve of the heart, it is the motor to the bronchial muscle. Some organs are innervated by one division only, e.g., the uterus and most arterioles are supplied by the sympathetic only, while the glands of stomach and pancreas by parasympathetic only.

The exact manner in which drugs influence the autonomic system is still obscure. Since the effects of some drugs resemble those following either stimulation or depression of the sympathetic or the parasympathetic systems, attempts have been made to explain their action as being due to their effects on the nerve-endings. In fact they act on an organ whose nerves have been divided and have degenerated and in which no nerve terminations exist. In view of the fact that nerve fibres are not influenced by most of the specific autonomic drugs, it is doubtful that the finer terminal fibrils, which are continuations of the axis cylinders, should be the seat of action of these drugs. Their action therefore must be exerted on some substance beyond the termini of the nerves. It has therefore been suggested that they act on the muscle cells directly, a fact rather difficult to reconcile, inasmuch as some drugs, notably adrenaline, act differently on different involuntary muscles inspite of the fact that they react uniformly to other stimuli. The natural conclusion out of this controversy is the assumption that there exists some intermediate structure between the nerve endings and the muscle, which has been differently named as "receptor substance," "myoneural junction" or "synapse." This theory even has been challenged on the ground that pilocarpine which stimulates the secretion of sweat and choline which causes contraction of the striped muscles are both antagonised by atropine, although there is no evidence of parasympathetic nerve-endings in these structures.

Dixon pointed out that after stimulation of the vagus nerve to the heart a substance could be extracted from the heart muscle which was inhibitory in its action on other hearts, and which effect could be antagonised by atropine, just as it antagonises vagus stimulation. This work was subsequently revived by Dale and Loewi, who have pointed out that these drugs act not by stimulating the nerve-endings but by liberation of certain chemical substances, *e.g.*, choline or adrenaline-like substance as the case may be. Loewi has shown that stimulation of vagus causes liberation of acetylcholine which acts directly on the cells, and that of sympathetic is followed by liberation of adrenaline. Drugs which

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stimulate the sympathetic act not because of the physical stimulation but by the formation of sympathetic hormone adrenaline around the cell. Similarly those stimulating the parasympathetic act by the formation of hormone acetyl-choline. Dale suggested that nerves which liberate at their terminals bodies resembling adrenaline or acetyl-choline should be called "adrenergic" or "cholinergic."

According to this theory atropine and ergotoxine act directly on the cells and render the tissues insensitive to acetyl-choline or adrenaline, thus preventing the effects of parasympathetic or sympathetic stimulation. But the explanation of the action of physostigmine is somewhat different. Pilocarpine, as is known, contracts the pupil after the degeneration of the 3rd nerve but not physostigmine. It has therefore been suggested by Loewi that physostigmine prevents the destruction of the ferment present in the blood and tissues which normally destroy acetyl-choline and therefore does not act on the denervated organs in which no acetyl-choline is liberated.

The result of sympathetic and parasympathetic stimulation on the different organs is set out in the following table. But it should be remembered that the function of certain nerves is still uncertain.

The effects of Sympathetic and Parasympathetic stimulation on different organs.

Organ	Sympathetic	Parasympathetic
Eye	Pupil: Dilatation from stimulation of the radiating fibres. Ciliary ms.: nil.	Pupil: contraction from stimulation of circular fibres. Ciliary ms.: contraction.
Bronchioles	Muscles: relaxation Glands: nil.	Muscles: contraction. Glands: increased secretion.
Alemintary canal	Relaxation, except the sphincters which contract.	Augmentation of peristalsis except the sphincters which relax.
Heart	Acceleration of rate.	Slowing of rate.
Arterioles	Constriction, except coronary vs. which dilate.	Nil as a rule.
Uterus	Mixed effect. Excitation or inhibition depending on the preponderance of particular nerves whether motor or inhibitory.	Nil.
Bladder	Relaxation, except the sphincter which contracts.	Contraction, except the sphincter which relaxes.

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Organ	Sympathetic	Parasympathetic
Salivary glands	Slight viscid secretion.	Increased secretion and vaso-dilatation.
Sweat glands	Though supplied by sympathetic they act as if they are supplied by parasympathetic. Therefore perspiration is induced by parasympathetic stimulants and inhibited by parasympathetic depressants. Possibly they receive augmentors from both sets, but the parasympathetic endings are accessible to the effects of drugs.	

Drugs acting on the sympathetic system.—The sympathetic fibres have two actions, *augmentor* and *inhibitor*. The augmentor effects are acceleration of the heart, vaso-constriction, dilatation of the pupil, increased secretion of saliva, tears, etc. The inhibitory effects are chiefly confined to the stomach, intestine, gall-bladder and the urinary bladder. It has also an inhibitory effect on the virgin uterus of cat.

(*a*) *Drugs which stimulate the sympathetic endings.*—Adrenaline, ephedrine and tyramine. Cocaine increases the peripheral excitability without directly stimulating it.

(*b*) *Drugs paralysing the sympathetic nerve-endings.*—Ergotoxine, ergotamine and apocodeine.

Drugs acting on the parasympathetic system.—With the exception of vagus this system is mainly augmentory. Parasympathetic stimulation causes slowing of the heart, contraction of the pupil, spasm of the bronchial muscles, increased secretion of all glands centrally innervated, *viz.*, sweat, saliva, stomach and pancreas, and contraction of the intestines, uterus and most plain muscles. The urine, secretion of bile, milk and the internal secretions are not affected by this system.

(*a*) *Drugs stimulating the parasympathetic endings.*—Muscarine, pilocarpine, physostigmine, acetyl-choline and anaphylotoxin.

(*b*) *Drugs depressing the parasympathetic endings.*—Atropine, hyoscine. They produce results opposite to stimulation.

Drugs Acting on the Eye

Drugs acting on the pupil.—The iris is the regulator of the pupil. It is composed of two sets of fibres, the circular which contract, and the radiating which dilate. These sets of muscles are in constant action, and by opposing each other constitute a sensitive balanced mechanism for the regulation of the size of the pupil. The sphincter iridis (circular fibres) is supplied by the 3rd or oculomotor, through the parasympathetic, which arise from the mid-brain, and the centre

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for the contraction of the pupil is located in the corpora quadrigemina. Stimulation of the 3rd nerve contracts, and its section dilates the pupil. The cervical sympathetic is the nerve for the radiating fibres; its stimulation causes dilatation and its division, contraction of the pupil. The oculomotor centre is kept under control by impulses passing from higher centres, and if these higher centres are inhibited, as during sleep, during surgical anæsthesia, and in opium poisoning there is contraction of the pupil (Mayer and Gottlieb).

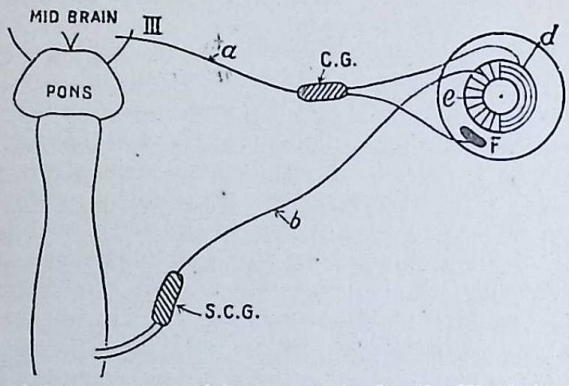

Fig. 1.—Explaining Action of Drugs on the Pupil. III.—3rd nerve showing the preganglionic parts and the endings supplying the circular fibres of the iris (d) and the ciliary muscles (F). S. C.G., superior cervical ganglion and sympathetic (b) supplying the radiating fibres of the iris (e).

Mydriatics or pupil dilators act as follows :—

1. *By paralysing the oculo-motor nerve-endings*, as atropine, hyoscine, homatropine, coniine, gelsemine.
2. *By stimulating the endings of the cervical sympathetic*, as cocaine, tyramine, adrenaline and ephedrine.
3. *By depressing the oculo-motor centre*, as in asphyxia (general anæsthetics, fourth stage).

Strong emotion, fear, excitement and asphyxia dilate the pupil either by stimulating some centres of the sympathetic nerve supplying the eye and simultaneous inhibition of the oculo-motor centre, or by stimulating the sympathetic supply of the adrenal gland and causing an increased secretion of adrenaline.

Myotics or pupil contractors act as follows :—

1. *By stimulating the endings of the third nerve*, as choline, pilocarpine, physostigmine, nicotine, muscarine.
2. *By stimulating the centre for contraction*, as opium, picrotoxin, general anæsthetics in the early stage. For action of opium, see *supra*.

Nicotine first stimulates and then depresses the ganglion cells of both the oculo-motor nerves, therefore the pupils first contract then dilate.

Drugs that impair accommodation.—Ciliary muscle adjusts the lens for distant and near objects of vision. During rest, the lens

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remains flattened, but to see near objects it becomes more convex owing to the drawing in of the ciliary processes by the contraction of the circular fibres. It is supplied by the 3rd nerve. Drugs that paralyse accommodation by acting on the ciliary muscle are called *cycloplegic;* they are atropine, gelsemine, pilocarpine, physostigmine.

Drugs affecting the intra-ocular tension.—The normal tension depends upon (*a*) the amount of intra-ocular secretion, (*b*) the freedom with which fluids may escape through the lymph channels (spaces of Fontana) into the canal of Schlemm. Tension may be raised by extra secretion, or by dilatation of the pupil which shuts off the spaces of Fontana.

1. *Drugs increasing the tension*, atropine, hyoscine and hyoscyamine.
2. *Drugs decreasing the tension*, pilocarpine and physostigmine.

1. Drugs Stimulating the Parasympathetic endings

Muscarine, an alkaloid derived from poisonous mushroom, *Amanita muscaria*, has the same pharmacological action as pilocarpine except that it produces more nausea and vomiting. It is not used therapeutically.

PILOCARPINE NITRAS

Pilocarpine Nitrate. $C_{11}H_{16}N_2O_2,HNO_3$

Source and characters.—The nitrate of an alkaloid, pilocarpine, obtained from the leaves of *Pilocarpus microphyllus* and other species of *Pilocarpus;* in white crystalline powder, soluble in 8 parts of cold water.

B.P. Dose.—$\frac{1}{20}$ to $\frac{1}{5}$ gr. or 0.003 to 0·012 grm.

Non-official Preparations

1. **Guttæ Pilocarpinæ.**—Pilocarpine Nitrate 0.5 to 1 p.c.
2. **Pilocarpine Hair Lotion.**—Pilocarpine Nitrate 2 grs., Quinine Hydrochloride 8 grs., Glycerin 2 drs., Aqua Rose 6 drs.
3. **Pilocarpinæ Hydrochloridum, U.S.P.**—Minute granular crystals. Soluble in alcohol and water. *Dose, U.S.P.*—0.005 grm. or $\frac{1}{12}$ gr.

Pharmacology

Pilocarpine is directly antagonistic to atropine in its effects upon the secretory nerves, the ends of the nerves governing the involuntary muscles, the ends of the vagus, and the ends of the third nerve in the eye. These effects are due to parasympathetic stimulation and will act even after the nerves are divided and allowed to degenerate.

Internally.—Pilocarpine readily enters the circulation and is carried to different structures, where it produces definite effects, which are described below under separate heads :—

Salivary Secretion.—Within about ten minutes after administration, pilocarpine produces a copious secretion of saliva of almost normal composition by directly stimulating the peripheral ends of the nerves supplying the salivary glandular cells, therefore it must act by stimulating the nerve-endings of the chorda tympani. It is a powerful

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sialagogue, the secretion amounting to a pint and a half, after one injection. The salivation is immediately stopped by injection of atropine.

Stomach and intestine.—The peristaltic movements of the unstriped muscles of the gastro-intestinal canal are increased by large doses owing to direct stimulation of the parasympathetic endings of the vagus, causing nausea, vomiting, colicky pain and diarrhœa. The pancreatic secretion is slightly affected, possibly due to muscular contraction of the duct, or indirectly through increased gastric secretion. The gastric juice and intestinal secretion are also increased. The biliary secretion is unaffected, but the spleen contracts.

Skin.—The next important action is on the skin. Within six to ten minutes after a hypodermic injection of pilocarpine nitrate ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) the face, neck and ears become flushed and drops of perspiration appear upon them, soon extending over the whole surface. The sweating is so profuse as to soak garments and bed clothes ; almost a gallon of sweat may thus be excreted by one diaphoresis. Therefore it is a **powerful sudorific.** The sweating is checked by atropine. The action is due to the stimulation of the nerve terminations in the glandular cells. It also stimulates the growth of hair, and makes it coarse and black.

Circulatory system.—Both the heart and pulse are accelerated at first, but are soon slowed and depressed. Quickening is the usual therapeutic effect when pilocarpine is given by the mouth. It excites both the vagal and sympathetic endings, and when given by the mouth the drug reaches the heart slowly and the sympathetic effect predominates ; whereas when a large dose is given directly into the circulation the vagal effect becomes marked and the heart is slowed. Atropine counteracts the slowing of the pulse, but it cannot do so if the vagus is cut ; thus showing that pilocarpine depresses the heart by stimulating parasympathetic endings of the vagus. It also depresses the heart directly, therefore the margin of safety is small, and its use has been followed by collapse and death. The blood-pressure falls from depression of the vaso-constrictor centre and the heart, though there may be a rise at first from vaso-constriction.

The number of white blood corpuscles (lymphocytes) is increased from contraction of the spleen muscles.

Respiratory system.—Pilocarpine increases both the nasal and bronchial secretions, and owing to the increased contraction of the bronchial muscles the breathing may be laboured. The respiratory centre is not affected directly by small quantities of pilocarpine, but the circulatory changes diminish the amount of blood passing through the lungs. These effects combined with the circulatory depression tend to promote œdema of the lungs, asphyxia, collapse and death.

Eyes. *(a) Pupil.*—Locally applied or given by the mouth

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or subcutaneously, it causes **contraction of the pupil.** This effect, which is prevented by the previous use of atropine, is due to stimulation of the myoneural junctions of the oculomotor nerve, and observed even after the nerves have degenerated. There is no stimulation of the sphincter muscle itself. It increases the flow of tears.

(*b*) *Accommodation.*—The ends of the third nerve in the ciliary muscle are stimulated, causing bulging of the lens and fixation of the eye in accommodation for near objects.

(*c*) *Intra-ocular tension.*—After a momentary rise the tension is diminished. This coincides with the contraction of the pupil and results from the increased escape of fluids which follow the opening of the spaces of Fontana.

Urinary tract.—Pilocarpine has no effect on the secretion of the urine, in fact the great loss of fluid by other channels causes a decrease in the amount of urine. Large doses given repeatedly produce glycosuria and diuresis probably by increasing the renal permeability. By its contractile effect on the bladder it causes suprapubic pain and irresistible desire to pass water.

Body heat and weight.—On account of the dilatation of the cutaneous vessels before sweating, there is a slight rise of temperature, but it soon falls during sweating. There is also a reduction of body weight to the extent of seven pounds or more.

Female generative organs.—Pilocarpine causes the uterine muscles to contract, sometimes to such an extent as to cause abortion. It also increases uterine and vaginal mucus. The secretion of milk is not affected, although earlier investigators claimed for it a galactagogue action. It is evident that the mammary glands do not possess any true secretory nerves.

Summary of action.—It will be observed that pilocarpine performs two most important specific functions, viz. :—(1) The *stimulation of secretion*, (2) the *contraction of the involuntary muscular fibres* due to stimulation of the nerve-endings and not to that of the muscular fibres themselves. *Salivation*, *diaphoresis* and *myosis* are the most marked effects. Children are less affected than adults.

Antagonists.—Belladonna and atropine. $\frac{1}{150}$ gr. of atropine given subcutaneously arrests profuse salivation and diaphoresis within 5 to 10 minutes.

THERAPEUTICS

Externally.—To promote the growth of hair, pilocarpine is largely employed in the form of hair lotion. In ophthalmic practice, it has been locally applied in iritis, retinitis, detachment of the retina, glaucoma, etc., but it is less active than physostigmine, and its effects more transitory.

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Internally.—Pilocarpine is chiefly employed for its diaphoretic action in **uræmia** and **uræmic convulsions**, where it may be the means of saving life by the elimination of urea and other products through perspiration. It is however now recognised that in uræmia other poisons than urea are responsible for the untoward symptoms, and the beneficial effect is due more to the improvement of circulation following removal of fluid which impairs kidney circulation, than to the elimination of the poison *via* the skin. It is of special service in **nephritis**. Under these conditions it promotes perspiration and secures functional rest to the kidneys and lowers blood-pressure. When there are **anasarca** and **serous effusions**, $\frac{1}{8}$ to $\frac{1}{2}$ gr. of pilocarpine nitrate produces profuse sweating and salivation, thereby relieving the waterlogged system which in its turn will cause an improvement in the kidney circulation resulting in its recovery. In cardiac dropsy it should be used with caution. Its use is often followed by weakness, languor, and general depression which may counterbalance any improvement following its use. The diaphoresis can be helped by wrapping the patient in warm blankets and giving him warm drinks. For its antagonistic properties it is used in poisoning by belladonna.

Caution.—Sometimes alarming prostration and collapse may follow the hypodermic injection of $\frac{1}{4}$ gr.; and atropine should at once be injected. It should be used with great caution in valvular diseases of the heart, fatty heart, emphysema and pleurisy, and the patient watched. It is contra-indicated in renal diseases associated with œdematous condition of the lungs, as by increasing bronchial secretion it may add to respiratory distress. Children are less affected than adults.

PHYSOSTIGMINAE SALICYLAS

Physostigmine Salicylate

Syn.—Eserine Salicylate.

Source.—The salicylate of an alkaloid, physostigmine, obtained from the seeds of *Physostigma venenosum*.

Characters.—Colourless, or faintly yellow, crystals, gradually acquiring a red tint on exposure to light and air. *Soluble* in about 100 parts of water, freely in alcohol (90 p.c.).

B.P. Dose.—$\frac{1}{100}$ to $\frac{1}{50}$ **gr. or 0.0006 to 0.0012 grm.**

Official Preparations

1. **Lamella Physostigminæ.**—Contains $\frac{1}{1000}$ gr. (0.065 mgrm.) of physostigmine salicylate in each.
2. **Oculentum Physostigminæ.**—Contains 0.125 p.c.

Non-official Preparation

1. **Guttæ Physostigminæ cum Cocaina, R.O.H.**—Physostigmine sulphate 0.25 and cocaine hydrochloride 1.25 in water 100.

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PHARMACOLOGY

Eye.—Applied locally to the conjunctiva, physostigmine is absorbed and produces the following changes—(1) **contraction of the pupil**; (2) **accommodation** for near objects due to the contraction of the ciliary muscle; (3) **diminished intra-ocular tension** due to the contraction of the pupil facilitating the escape of the fluid by allowing it freer access to the spaces of Fontana. All these actions are due to the *direct stimulation of the parasympathetic endings of the third nerve*, but not to the paralysis of the sympathetic, as is shown by the following observations:—

1. The pupil contracted by physostigmine will dilate if suddenly shaded, or if the cervical sympathetic is stimulated.
2. The contraction produced by physostigmine is much greater than that caused by section of the sympathetic.

It follows therefore that the myosis is not due to paralysis of the sympathetic, but to stimulation either of the oculo-motor nerve-endings or the sphincter itself. *The following considerations show that it is the nerve-endings that are concerned.*

1. The pupil dilated by atropine can be made to contract with physostigmine to a small extent but less than when applied to an unatropinised eye.
2. Physostigmine fails to produce contraction of the pupil after degeneration of the third nerve, although the muscle of the iris is intact and can be made to respond to electrical stimulation or other drugs.

Internally. **Mouth.**—Physostigmine **increases the salivary secretion** by stimulating the endings of the chorda tympani. The effect is not central as the secretion can be induced after section of the nerves, and since the secretion is not checked after administration of nicotine, salivation cannot be from any action on the ganglion cells, which are paralysed by nicotine. But if the nerves are paralysed by the previous use of atropine it fails to produce any secretion.

Stomach and intestines.—It is readily absorbed by the stomach and increases the gastric and intestinal movements by stimulating the vagus endings. In therapeutic doses the peristaltic movements become more active, consequently there may be vomiting, and since the intestinal contents are hurried down, there is diarrhœa with watery stools.

Heart and circulation.—In small doses it increases the contractile force of the heart, causing slowing of the pulse and rise of blood-pressure. In large doses the slowness is increased although the blood-pressure falls. This action is due to excitability of the peripheral terminations of the vagus in the heart and direct action on the cardiac muscle.

The blood-pressure rises from the increased contractile force of the heart aided partly by (*a*) the contraction of the

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arteries by the direct effect on the muscular coat; and partly by (*b*) the tetanic contraction of the intestinal tract thus expelling the blood from the mesenteric area.

Respiration.—This is at first quickened but soon depressed. The acceleration is caused (1) by the stimulation of the respiratory centre of both the medulla and the cord; (2) by the stimulation of the peripheral terminations of the vagus in the lungs; and (3) by the spasmodic contraction of bronchial tubes producing partial asphyxia. Death takes place from failure of the respiratory centre.

Nervous system.—The motor cerebral cortex becomes more excitable causing epileptiform convulsions; these have been attributed to partial asphyxia caused by respiratory paralysis and bronchial constriction. In large doses it depresses the central nervous system beginning from the cord and spreading upwards, so that consciousness is not affected even by toxic doses, and the mind remains clear to the last. The pupils may be contracted, but not as a rule to any great extent. The respiratory centre is stimulated first as mentioned before.

Muscles.—Marked fibrillary contraction of the voluntary muscles is often seen. This is due to the stimulation of nerve-endings of the striated muscles for it takes place when the nerves have been divided, but disappears if the motor nerve-endings are paralysed by curare but not by atropine and does not occur after the nerve ends have degenerated. It has therefore been suggested that it acts on the motor end-plates of the voluntary muscle. The sensory nerves remain unaffected. The involuntary muscles of almost every organ such as the stomach, intestines, bladder, heart, arteries, spleen, uterus, iris, etc., are stimulated producing powerful contraction. All these effects are due to the action of physostigmine upon the parasympathetic endings. (*See* page 216).

Secretions.—Not only saliva, but sweat, tears and buccal mucus are increased in much the same way as with pilocarpine but the action is not so powerful. The secretion of adrenaline is also increased. The secretion of milk, bile and urine is not affected.

Elimination.—Physostigmine is excreted by the liver and salivary glands not by the kidneys.

Antagonists.—Atropine, chloral, strychnine and morphine.

Toxicology.—Poisoning by physostigmine is rare. Emetics or pump. Stomach wash with 0·2 p.c. potassium permanganate. Atropine $\frac{1}{30}$ gr. hypodermically till the pupils dilate well. Strychnine if necessary. Artificial respiration overcomes repiratory trouble.

THERAPEUTICS

Eye.—Eserine is chiefly used (1) to contract the pupil in photophobia, and diminish the amount of light falling on a sensitive retina; (2) to break up adhesions in iritis; (3) to

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prevent prolapse of the iris after corneal wounds, ulcers or perforation; (4) to reduce intra-ocular tension in glaucoma and perforating keratitis; (5) to stimulate the paralysed ciliary muscles and iris; (6) in detachment of the retina; and (7) to antagonise the effects of atropine, homatropine and cocaine on the pupil. It is generally used in $\frac{1}{2}$ to 1 p.c. solution, 2 to 4 drops being dropped into the eye at a time.

For its depressing effect on the central nervous system it has been used in several convulsive diseases, chiefly tetanus, chorea, etc., but without any appreciable benefit. As it increases intestinal peristalsis its use has been extolled in atony of the intestine, tympanites, post-operative intestinal paralysis, and chronic constipation. In all these conditions it is administered subcutaneously ($\frac{1}{80}$ gr.).

CHOLINE

(Not Official)

A syrupy liquid occurs in organ extracts, many vegetables, ergot, and as a decomposition product of lecithin. It has been isolated from washed portions of intestines of rabbit, dog and cat.

Action and Uses

Choline has three important actions, *viz.* (1) it *dilates the vessels* and causes a fall of blood pressure; (2) *stimulates parasympathetic endings (see* page 215); and (3) *first stimulates and then paralyses the autonomic ganglia* (nicotine effect). After an injection of atropine it produces a rise of pressure. It weakens and slows the heart through stimulation of the vagus, this is also counteracted by atropine and adrenaline.

It is present in many tissues, and it is believed that its presence, which is of the nature of hormone, maintains the normal activity of the intestine. It increases gastric secretion by stimulating the secretory endings of the vagus in the stomach. Choline is largely used in the form of Choline Hydrochloride *(dose,* 0·6 grm. or 10 grs.), or as Acetylcholine, (*dose,* $\frac{3}{4}$ to $1\frac{1}{2}$ grs). These are more powerful than choline. Leubret and Pery *(British Medical Journal, Epitome,* May 10, 1930) have shown that in all cases of tuberculosis there is marked decrease of blood cholesterol, and sometimes also in the blood sugar, showing a deep humoral trouble. They recommended injection of *Choline Hydrochloride,* 2 cgm. ($\frac{1}{3}$gr.) in 1c.c. in all stages of **tuberculosis** and reported favourable result. The treatment is followed by a lowering of temperature, a return of the appetite with a re-establishment of the digestive functions and a gain in weight. The blood cholesterol is increased and the blood-sugar-cholesterol ratio returns to normal. When combined with calcium it gives better result in tuberculosis. The usual formula is calcium gluconate 10 p.c. and choline hydrochloride $\frac{1}{30}$ gr. in 10 c.c. of

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physiological solution. This is sold under the name of Injectable Calcinol. The injections are given once or twice a week.

Acetyl choline is used to **lower blood-pressure** in an emergency, and it will keep the pressure down for several hours, when given in doses of 0·05 to 0·1 grm daily. It is also recommended in **Raynaud's disease** and checks the **night sweats of phthisis.** It should always be used *intramuscularly*, intravenous injection is dangerous, and given by the mouth it is useless. Subcutaneous injection of Sodium Cholate, 0.05 to 0.1 grm. in strictly isotonic solution has also been used successfully in the treatment of **arterial hypertension.**

It has been used intramuscularly to counteract **paralysis** of the **intestine** such as occurs after laparotomy and intestinal operations. It may also be used to relieve severe post-operative gas distention and pain.

2. Drugs Depressing the Parasympathetic endings

BELLADONNAE FOLIUM

Belladonna Leaf. N.O. *Solanaceæ*

Syn.—Deadly Nightshade Leaves.

Source.—The leaves and tops of *Atropa Belladonna*, collected when the plant is in flower, and dried. Contains not less than 0·3 p.c. of the alkaloids of the leaf, calculated as hyoscyamine.

Characters.—Leaves alternate below, in unequal pairs above; 5 to 25 cm. long, broadly ovate, acute, entire, glabrous, short stalked. Corolla gamopetalous, campanulate, purple.

Composition.—(1) *Atropine.* (2) *Hyoscyamine*, 0.4 p.c. This is more abundant than atropine. It is lævorotatory, but otherwise allied to atropine.

Official Preparations

1. **Belladonna Pulverata.** *Syn.—Pulvis Belladonnæ.*—Leaf reduced to fine powder and adjusted, if necessary, by admixture of powdered exhausted belladonna leaf to contain 0·3 p.c. of alkaloid hyoscyamine. $\frac{1}{100}$ gr. of alkaloid in 3 grs. **B.P. Dose.—½ to 3 grs. or 0.03 to 0.2 grm.**
2. **Extractum Belladonnæ Siccum.**—Alkaloid 1 p.c. or $\frac{1}{100}$ gr. in 1 gr. **B.P. Dose.—¼ to 1 gr. or 0.015 to 0.06 grm.**
3. **Tinctura Belladonnæ.**—Contains 0.03 p.c. w/v of the alkaloid, or $\frac{1}{100}$ gr. in 30 ms. **B.P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

BELLADONNAE RADIX

Belladonna Root

Source.—The dried root of *Atropa Belladonna.* Contains not less than 0·4 p.c. alkaloid hyoscyamine.

Characters.—In cylindrical pieces, entire or longitudinally split up to 4 cm. in diameter at the crown; pale greyish-brown and wrinkled longitudinally. Fracture short. Internally white, starchy with no radiate appearance.

Composition.—The same as that of the leaves *(see above).*

B.P. Dose.—½ to 2 grs. or 0·03 to 0·12 grm.

Official Preparations

1. **Emplastrum Belladonnæ.**—Alkaloids 0.25 p.c.
2. **Extractum Belladonnæ Liquidum.**—0.75 p.c. of the alkaloids

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of the root, or $\frac{1}{150}$ gr. in 1 m. **B.P. Dose.**—$\frac{1}{4}$ **to 1 m. or 0·015 to 0·06 mil.**

3. **Linimentum Belladonnæ.**—Alkaloids 0.375 p.c.

4. **Suppositorium Belladonnæ.**—Alkaloids $\frac{1}{60}$ gr. (0.001 grm.) in each; or $2\frac{1}{2}$ ms. of the liquid extract.

Non-official Preparations

1. **Collodium Belladonnæ, B.P.C.** *Syn.—Empl. Belladonnæ Fluidum.*—Liquid extract 50, Canada turpentine 4, castor oil 2, camphor 1.5, pyroxylin 2.5, alcohol (90 p.c.) 10, ether to 100.

2. **Extractum Belladonnæ Viride, B.P.C.**—A soft extract made from the leaves, containing 0.95 to 1.05 p.c. of the alkaloids of belladonna. *Dose.*—$\frac{1}{4}$ to 1 gr. or 0.016 to 0.06 grm.

ATROPINA

Atropine. $C_{17}H_{23}NO_3$

Source.—An alkaloid, *dl*-hyoscyamine, obtained from *Atropa Belladonna*, *Hyoscyamus muticus*, and other plants of the family Solanaceæ.

Characters.—In colourless crystals, odourless. *Solubility.*—1 in 500 of water, readily in alcohol (90 p.c.), chloroform and ether. The solution is *alkaline.*

Incompatibles.—Caustic alkalies and mercurial salt.

B.P. Dose.—$\frac{1}{240}$ **to** $\frac{1}{60}$ **gr. or 0·00025 to 0·001 grm.**

Non-official Preparations and Derivatives

1. **Ung. Atropinæ cum Cocaina, R.O.H.**—Atropine 4 gr., Cocaine 8 gr., Soft Paraffin 1 oz. Mix by heat. In ophthalmic practice.

2. **Oculentum Atropinæ et Cocainæ, B.P.C.**—Atropine sulphate $1\frac{1}{4}$ gr.; cocaine hydrochloride $2\frac{1}{2}$ gr.; water q.s.; simple eye ointment, q.s. 500 gr.

3. **Euphthalmine.** *Syn.—Hydrochloride of n-Methyl-diacetone-alkamine.*—A synthetic compound. A 5 to 10 p.c. solution dilates the pupil like homatropine, but its effects are not so lasting.

ATROPINAE SULPHAS

Atropine Sulphate. $(C_{17}H_{23}NO_3)_2,H_2SO_4,H_2O$

Source.—The sulphate of the alkaloid atropine.

Characters.—In colourless crystals. *Solubility.*—1 in 1 of water, 1 in 4 of alcohol (90 p.c.). The solution is *neutral.*

B.P. Dose.—$\frac{1}{240}$ **to** $\frac{1}{60}$ **gr. or 0·00025 to 0·001 grm.**

Official Preparations

1. **Lamella Atropinæ.**—Each contains $\frac{1}{5000}$ gr. (0·013 mgrm.).

2. **Oculentum Atropinæ.**—0·25 p.c.

3. **Oculentum Atropinæ cum Hydrargyri Oxido.**—Atropine sulphate 0.125 p.c., yellow mercuric oxide 1 p.c.

HOMATROPINAE HYDROBROMIDUM

Homatropine Hydrobromide. $C_{16}H_{21}NO_3,HBr$

Source.—The hydrobromide of an alkaloid, homatropine, prepared from tropine and mandelic acid.

Characters.—A colourless crystalline powder; odourless. *Soluble* in 6 parts of water, in 18 parts of alcohol (90 p.c.).

B.P. Dose—$\frac{1}{64}$ **to** $\frac{1}{32}$ **gr. or 0.001 to 0.002 grm.**

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Official Preparation

1. **Lamella Homatropinæ.**—$\frac{1}{100}$ gr. (0·65 mgrm.) in each.

Pharmacology

Externally.—The unbroken skin absorbs the alkaloids of belladonna if combined with alcohol, chloroform, glycerin or fat. Exposed mucous surfaces and raw skin absorb them more rapidly. Both belladonna and atropine powerfully paralyse the peripheral terminations of the sensory nerves, especially if there is pain, and are therefore **local anæsthetics** and **anodynes**. To a much less extent they paralyse the motor and secretory nerve-endings. The blood vessels of the part first contract and then dilate.

Internally.—Atropine readily enters the blood and circulates unaltered without affecting the blood corpuscles. It chiefly affects the nervous system; other organs and tissues are indirectly influenced through its action on their special or secretory nerves. Therefore we will first notice its action on the nervous system proper and afterwards on other organs of the body.

Nervous system.—Its effects on the central nervous system are those of general stimulation. But it acts more powerfully on the higher divisions of the nervous axis, so that in cases of poisoning the symptoms are referred more to the brain, and consist in increased co-ordinated movements like delirium and talkativeness, whereas with strychnine, which also stimulates the central nervous system, the symptoms arise from stimulation of the lower axis of the nervous system and consist of exaggerated reflexes and convulsions.

1. *Cerebrum.*—In medicinal doses belladonna scarcely produces any effect on the convolutions, but in large doses it stimulates the central motor area causing general nervous excitement, talkativeness, mental hallucination, disordered gait and vision. The conjunctiva and face become flushed, pulse is quickened and respiration rendered frequent. Still larger doses aggravate the symptoms causing delirium and convulsion followed by stupor and coma. The reflexes become more active but the higher psychical faculties are not affected like caffeine.

2. *Medulla and cord.*—Two chief centres are powerfully stimulated by belladonna, *viz.* (*a*) the respiratory; and (*b*) the vaso-motor. The vagal centre is affected to a much less extent. It also slightly increases then diminishes the reflex excitability.

3. *Sensory nerves.*—Belladonna, whether locally applied or given by the mouth, paralyses the peripheral terminations of the sensory nerves and thereby relieves pain if present. It is therefore a **local** and **general anodyne**. Its action is

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not so powerful as that of atropine. As a general anodyne atropine is inferior to morphine.

4. *Motor nerves and voluntary muscles.*—The motor nerves are slightly paralysed towards the end, but the voluntary muscles are never affected.

5. *Stomach and intestine.*—In the stomach atropine relieves pyloric spasm without interfering with the normal movements of the stomach. In ordinary therapeutic doses however the normal movements are not influenced nor the effects of purgatives interfered with, but it relieves the griping pains and irregular movements of the gut by directly depressing the vagal endings. It was formerly supposed that these effects were due to the paralysis of the terminations of the extrinsic nerves of the stomach and intestine. In large doses, as used in animal experiments, atropine increases peristalsis from its effects on the Auerbach's plexus.

6. *Bladder, urethra, uterus, etc.*—The terminations of the nerves supplying the involuntary muscles of the bile duct, bladder, ureter, vesiculæ seminalis, uterus, vagina, are paralysed. Atropine therefore relieves spasm of these organs, and in cases of bile duct and ureters help passage of calculi.

7. *Third nerve in the eye.*—Atropine has the following important effects on the eye: (*a*) *The pupil.*—The pupil is regulated by the iris which is composed of two sets of muscular fibres—the circular which contract and the radiating which dilate. The former is supplied by the third nerve and the latter by the sympathetic fibres from the superior cervical ganglion (*see* fig. 1, page 218). Dilatation of the pupil may be due to either depression of the sphincter iridis or stimulation of the radiating fibres ; while contraction results from the opposite influences. These stimulations or depressions may be of centre, ganglia, nerve-endings, or muscle fibres. Atropine administered internally **dilates the pupils** and when dropped into one eye it dilates the pupil of that eye, but has no effect on the other eye ; further, stimulation of the third nerve, either central or peripheral to the ciliary ganglia is without any effect on the pupil. Dilatation is due to the paralysis of the parasympathetic endings of the 3rd nerve, and since the direct stimulation of the sphincter iridis results in contraction it has no effect on the muscle. Dilatation caused by atropine is however not maximum for stimulation of the cervical sympathetic results in further dilatation of the pupil, and that after the removal of the superior cervical ganglion and subsequent degeneration of the sympathetic nerve fibres, atropine fails to dilate the pupil.

(*b*) *Accommodation.*—Atropine paralyses the terminations of the third nerve in the ciliary muscle and thus **paralyses accommodation.** It is therefore strongly cycloplegic.

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(*c*) *Intra-ocular tension.*—As an indirect result of the dilatation of the pupil by which the flow of lymph is obstructed, atropine **increases intra-ocular tension.**

8. *Vagal endings in the heart.*—The vagus is the inhibitory nerve of the heart. Belladonna stimulates the vagus centre causing slowing of the pulse, but this is quickly followed by depression of the vagus nerve-endings, rendering the **pulse-beat more rapid.** This rapidity cannot be diminished by stimulating the vagus. At times the excitement becomes so strong that the heart-sounds may be heard a few feet from the patient. With the acceleration of the pulse belladonna does not reduce the force and tone of the heart. Since the inhibitory fibres are almost inactive at birth, atropine has no effect in increasing the heart beat in the new born child. It has also little effect in old age. The vagus effect shows both at the sinus and the auriculo-ventricular nodes, and atropine therefore checks heart-block caused by digitalis. Sollmann has shown that atropine has some action on the cardiac muscle, which can be observed in the isolated heart and on the nerve-free heart of embryonic chick.

9. *Vagal endings in the bronchial walls.*—Both the afferent and efferent terminal filaments of the vagus are paralysed after a brief stimulation, producing relaxation of the muscular coat of the tubes, and diminishing the sensibility and reflex action (paralysis of the afferent fibres). These are the only effects produced in therapeutic doses. Thus belladonna is a **bronchial antispasmodic.** The sympathetic fibres which dilate the bronchi are unaffected by atropine. It also diminishes the bronchial secretion.

In large doses the respiration becomes quicker and deeper by the stimulation of the respiratory centre and increased formation of CO_2, but toxic doses paralyse it and make it shallow and slow.

10. *Vaso-motor nerves and the skin.*—The action of belladonna on the blood-pressure depends on its effect on the heart. After a temporary fall the pressure rises above normal partly from its effect on the heart and partly from stimulation of the vaso-motor centre. The rise of blood-pressure is greater if it has been lowered by excessive vagus stimulation of the heart and dilatation of the blood vessels. In toxic doses the vaso-motor centre is paralysed and the blood-pressure falls. The arteries of the skin, especially those of the head and neck, are dilated in toxic doses giving rise to flushing of the face, or scarlatiniform or erythematous rash on the skin so often seen in belladonna poisoning. Some patients are specially susceptible to belladonna and a single therapeutic dose causes flushing of the skin and dryness of the mouth. This is due to idiosyncrasy.

11. *Secretory nerves.*—Atropine is a powerful paralyser

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of almost all the secretory nerve-endings in the body, thereby exercising a most powerful depressant influence on the secretions of most of the secretory organs. Its actions on these organs are given below :—

(*a*) *Salivary and mucous glands.*—Even in small doses atropine powerfully paralyses the terminations of the secretory fibres of the chorda tympani, but not the vaso-dilator ones, so that stimulation of the chorda tympani does not increase the flow of saliva from the submaxillary gland though its vascularity is increased. Stimulation of the sympathetic still induces secretion, this shows that although the secretory nerves are paralysed secreting cells are not influenced in any way. It also depresses the terminations of the secretory nerves of the salivary and mucous glands. Consequently, the mouth, palate and throat become dry and red. After large doses the dryness increases so much that deglutition becomes impossible. Hence atropine is a powerful **antisialagogue.**

(*b*) *Gastro-intestinal glands.*—Atropine paralyses the terminations of the secretory fibres of the vagus in the stomach, and reduces or even arrests the gastric secretion. The hydrochloric acid is more reduced than pepsin or the fluid as a whole.

(*c*) *Liver and pancreas.*—Secretion of the pancreas depends upon the presence in the blood of secretin rather than on nerve impulse, and since it reduces the secretion of hydrochloric acid in the stomach which in the duodenum acts as stimulant to the formation of secretin, there is some diminution in the secretion of the pancreatic juice. The secretion of bile is little affected by atropine.

(*d*) *Bronchial glands.*—The secretion of the bronchial and tracheal mucus is very much diminished.

(*e*) *Sweat-glands.*—Given by the mouth atropine powerfully checks sweating. This it does by paralysing the terminations of the secreting nerves. The skin therefore becomes dry and hot. Applied locally it has no influence over the secretion of the sweat.

(*f*) *Mammary glands.*—The secretion of milk is also arrested, but this is doubtful since the secretion of milk is largely independent of the central nervous system.

(*g*) *Lachrymal glands.*—Prolonged use of atropine arrests their secretion.

(*h*) *Kidneys.*—Here its action is uncertain. Since the kidneys are not controlled by any secretory nerves, atropine has very little effect on the amount of urine. Large doses cause retention of urine as the result of paralysis of the bladder.

Temperature.—Belladonna in moderate doses raises the temperature of the body by 3 to 4 degrees due possibly to suppression of perspiration. As the circulation fails the temperature falls.

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Elimination.—Atropine is excreted unaltered by the urine within 10 to 20 hours. It increases urea, phosphates, sulphates, but not chlorides in the urine.

Toleration.—Children can bear large doses of belladonna. Old people bear it badly. *Idiosyncrasy* to the drug is common, some patients showing flushing, dryness of the mouth and throat and an erythematous rash even with ordinary therapeutic doses. This is often noticed amongst members of the same family, all the members being susceptible to it.

Summary of action.—1. Atropine stimulates the following centres:—(*a*) cerebral, producing delirium; (*b*) vital medullary centres—respiratory, vagal and vaso-motor. 2. It depresses (*a*) the sensory nerve-endings; (*b*) the motor nerve-endings in the smooth muscles of the viscera, thus allays abnormal contractions of the muscles of the bronchi, stomach, intestine, bile duct, etc.; (*c*) the parasympathetic endings of the third nerve of the eye; and (*d*) the vagus nerve-endings—making the heart free from the inhibitory nerve control.

Methyl and ethyl atropines do not cause tetanus in frogs and paralyse the motor ends, but they act like atropine on the eye, heart, etc.

Acute toxic action.—The symptoms that follow a moderate dose of atropine are (1) dry mouth and throat, (2) dilated pupil, (3) dim vision, (4) dry skin, (5) dysuria, (6) dysphagia, (7) delirium (wild). Erythematous rashes are common. At the *post-mortem* all organs are in a state of venous congestion due to asphyxia.

The symptoms of poisoning have been observed after the application of plaster, glycerin of belladonna, or liniment.

Treatment.—Emetics or pump. Tannin, tea, charcoal; morphine in the early stage, caffeine, or pilocarpine ¼ gr. hypodermically, repeated till the mouth becomes moist. Physostigmine or chloral hydrate are also recommended. Stimulants, hot bottles, artificial respiration. Ice to the head for delirium. As the poison is eliminated by the urine, the bladder should be emptied now and then to prevent reabsorption.

Physiological antagonists.—Morphine, pilocarpine, physostigmine, aconitine, chloral hydrate, hydrocyanic acid, muscarine, etc. Of these the first three are the most powerful.

THERAPEUTICS

Externally. **Skin.**—As a local *anodyne*, the liniment, plaster or ointment is largely employed to soothe irritability or pain in **neuralgia, soreness of muscles**, etc. Chloroformum belladonnæ (1 of liquid extract in 2), or ung. atropinæ are most powerful in this respect. Occasionally atropine injected subcutaneously as near the nerve as possible does more good in neuralgia, especially in **sciatica**, than any local application. Glycerinum belladonnæ or collodium belladonnæ may be applied over threatening boils, abscesses, etc. Liniment of belladonna rubbed in three or four times a day, or a hypodermic injection of atropine in obstinate

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cases, checks local sweating. In the form of an ointment either alone or better still with conium, belladonna lessens the spasm of **anal fissure** and the pain and irritation of **piles.**

Female diseases.—The plaster or the extract with glycerin is used to stop the secretion of milk. But the same results are obtained by the application of simple adhesive plaster, or yellow wax and olive oil. Extract of belladonna with glycerin (5 to 10 grs. to 1 oz.) in cotton wool may be used as a tampon in inflammation of the womb or cervix. A pessary containing the extract 2 grs., tannic acid 7 grs., and cocoa-butter *q.s.*, is very serviceable in leucorrhœa with ulcerated os. A suppository containing extract 1 gr. is an excellent application to relieve the pain of spasmodic and neuralgic dysmenorrhœa.

Eye.—A solution of atropine is dropped into the eye to dilate the pupil to facilitate examination of the internal eye posterior to the pupil, and paralyse the accommodation in fitting glasses. Smaller doses (0.1 to 0.01 p.c. solution will dilate the pupil but stronger solution (1 p.c.) is required to paralyse accommodation. As a rule accommodation does not recover till after 5 to 7 days, and the pupil does not become normal till after one to two weeks. Where only temporary mydriasis is required, as in estimating errors of refraction, homatropine may be used in preference to atropine as the effects pass off more quickly and there is less likelihood of toxic effects from absorption. In inflammatory conditions it is applied to give rest to the iris and ciliary muscle, and in iritis to prevent formation of adhesions to the lens and cornea. It is contra-indicated where there is suspicion of glaucoma as by increasing intra-ocular pressure it may either aggravate the disease already present or may precipitate an acute attack.

Internally.—Atropine is indicated in all conditions where a depression of the parasympathetic nerve-endings is required. It is therefore used to diminish secretion of sweat, saliva, or tears ; to reduce spasm of involuntary muscles, *e.g.*, of bronchi, stomach, intestine, sphincter of the gall-bladder, urinary bladder and uterus ; and to stimulate the respiratory centre.

Alimentary canal.—Atropine sometimes checks mercurial salivation. In small doses, frequently repeated, alone or in combination with aconite, belladonna (Tr.) checks acute tonsillitis. As it lessens the secretion of gastric juice and the motor activity of the stomach, atropine may be used in hyperchlorhydria, gastric ulcer, etc., and is specially valuable in acute conditions with severe pain. The extract is often combined with purgatives either to increase their activity or lessen griping. It has been used with some success in some forms of constipation, and may be given in

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habitual or chronic constipation and painful defæcation. In obstinate constipation Trousseau recommends the extract $\frac{1}{6}$ to $\frac{1}{4}$ gr., night and morning.

In full doses ($\frac{1}{60}$ gr.) atropine is useful in sea sickness where it acts by paralysing the vagus. In fact persistent vomiting often results from pyloric spasm which is checked by atropine.

Belladonna is often effective in **intestinal obstruction** due to fæcal stasis, atony of the intestine and reflex stricture; but to be of any use it should be given in large doses (20 to 30 ms.) frequently till the symptoms of poisoning appear. Alone or with opium it is useful in peritonitis, enteritis and appendicitis. It also relieves the pain of biliary, intestinal and lead colic by paralysing the sensory nerve-terminations and relaxing the involuntary muscular fibres, and since it does not cause constipation it is preferable to morphine specially in lead colic. A hypodermic injection of atropine ($\frac{1}{20}$ gr.) often helps reduction of hernia or volvulus.

Heart and circulation.—Belladonna relieves palpitation, pain and distress of the heart. For this purpose a plaster is often applied over the cardiac region. In cases where a patient with a weak heart is to be placed under chloroform, atropine may be injected subcutaneously to stimulate the respiratory centre and to prevent excessive reflex vagus stimulation at the onset. It is used in **bradycardia** or **partial heart-block**, but has no effect in complete and permanent heart-block. On the other hand when the slowness of the heart is due to disease of the muscle itself atropine is of no use. In fact its use has been suggested as a means of diagnosis between myogenic and neurogenic bradycardia. In these cases atropine must be pushed to the limit of physiological tolerance. As it has very little effect on the pulse in typhoid fever where the heart muscle is affected by the toxin, it has been used to differentiate typhoid from other fevers.

Respiratory tract.—Belladonna is extremely useful in many spasmodic affections of the air-passages, such as **asthma, spasmodic bronchitis** and **whooping cough**. A subcutaneous injection of atropine often gives great relief in spasmodic asthma. In whooping cough it must be given freely before we may expect any decided improvement. In nasal catarrh with profuse discharge atropine gives immediate relief. As it stimulates respiration it may be used in pneumonia, in narcotic poisoning, and as a preliminary to ether anæsthesia; and is often combined with morphine to counteract the depressing effect on respiration of the latter. It has also been used to prevent **anaphylaxis.**

Skin.—Atropine (1 to 2 ms. of the solution, or $\frac{1}{180}$ gr. hypodermically) arrests excessive sweating. It is therefore an excellent remedy for night-sweats of phthisis.

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Nervous system.—Belladonna is now rarely used in nervous diseases. It sometimes controls **delirium** in fevers. Atropine is used in the treatment of **post-encephalitic Parkinsonism** where it gives great relief by diminishing muscular rigidity, reducing tremors, and lessening excessive lachrymation and salivation. The method consists in ascertaining the *maximum dose* that causes improvement by a daily graduated increase of dose. When such increase yields no further benefit, the dose is similarly decreased until the return of the symptoms show that the dose is too small. Begin with a total daily dose of 0.5 mgrm ($\frac{1}{120}$ gr.) in two doses, and increase by 0.5 mgrm. daily spread over three doses till no further improvement is noticed, keep on at this maximum dose for a few days, then reduce the dose by 0.25 mgrm. daily until a point is reached at which subjective and objective symptoms return. A slightly higher dose than this is the *optimum dose*. In mild cases the optimum dose is 3 to 8 mgrm. ($\frac{1}{20}$ to $\frac{1}{8}$ gr.) daily; in severe cases it varies from 12 to 24 mgrm.

Genito-urinary tract.—It is a very useful remedy in **incontinence of urine** in children, and retention from over-activity of the sphincter of the bladder. Here it acts by relaxing the spasmodic contraction of the bladder. It may stop **nocturnal emissions** in persons whose genitals are weak and relaxed, and when discharge takes place without dream or orgasm. But extract of hyoscyamus and camphor are better for this purpose. It is very useful in allaying the pain and helping the expulsion of **renal calculus**, but in order to obtain these effects it must be given in large doses until toxic action is produced (W. Murray). Cystitis, dysuria, urethral spasms and, in fact, any kind of pain in the pelvic organs, *e.g.*, **dysmenorrhœa**, can be removed by belladonna either administered in the form of a suppository or by the mouth.

Antidotes to poisons.—Atropine may be successfully used as a physiological antidote in poisoning by morphine, physostigmine, chloroform, aconite, poisonous mushrooms (muscarine), nitroglycerin, pilocarpine, gelsemine and hydrocyanic acid.

Prescribing hints.—A porous belladonna plaster is the best to use as it causes less itching and irritation. Collodion belladonna may be painted over an uneven surface in its stead. Atropine may be given in tablets, pills or in solution. Hypodermically it is often combined with morphine to counteract its unpleasant physiological effects and to increase its sedative virtue. 10 ms. of the tincture every 4 hours to young children for *whooping cough*; and 30 to 40 ms. of the same every 1 or 2 hours during an *attack of renal colic* until atropism—dryness of the throat, dilatation of the pupils and delirium—sets in are not unsafe to use in these cases. Caustic

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fixed alkalies destroy the alkaloids of belladonna, but carbonates and bicarbonates of sodium and potassium do not do so.

Homatropine hydrobromide may be applied into the eye either in solution (4 grs. in 1 oz. of water), or as a disc, or dissolved in castor oil with cocaine. The object of mixing it with castor oil is to prevent it from being washed away by the tears. As it dilates the pupil more quickly (within an hour) and the effects are of shorter duration (passing off within 24 hours), it is used in preference to atropine, moreover it has less tendency to increase intra-ocular tension. It is therefore a more convenient drug for examination of the eye, unless it is desired to paralyse completely the ciliary muscles.

HYOSCYAMUS

Hyoscyamus

Syn.—Henbane Leaves ; Hyoscyami Folia.

Source.—The dried leaves and flowering tops of *Hyoscyamus niger*. Contains not less than 0·05 p.c. of the alkaloid hyoscyamine.

Characters.—Leaves vary in length up to 25 cm., mostly sessile ; exstipulate, triangular-ovate or ovate-oblong, acute, sinuate, pale green. Furnished with glandular hairs particularly underneath. Branches cylindrical and glandular hairy, corolla yellow ; odour strong ; taste, bitter and slightly acrid when fresh.

Composition.—Chief alkaloids are (1) *Hyoscyamine*, this is converted into *Atropine* on keeping. (2) *Hyoscine* (Scopolamine). (3) A poisonous oil.

Incompatibles.—Liquor potassæ, lead acetate, silver nitrate, and vegetable acids.

B.P. Dose.—3 to 6 grs. or 0·2 to 0·4 grm.

Official Preparations

1. **Extractum Hyoscyami Liquidum.**—Contains 0·05 p.c. w/v of the alkaloid hyoscyamine, or $\frac{1}{3\frac{1}{7}0}$ gr. in 6 ms. **B.P. Dose.—3 to 6 ms. or 0·2 to 0·4 mil.**

2. **Extractum Hyoscyami Siccum.** *Syn.—Extractum Hyoscyami.* —0·3 p.c. of the alkaloid hyoscyamine, or $\frac{1}{3\frac{1}{5}0}$ gr. in 1 gr. **B.P. Dose.—$\frac{1}{4}$ to 1 gr. or 0.016 to 0·06 grm.**

3. **Tinctura Hyoscyami.**—Contains 0·005 p.c. w/v of the alkaloid hyoscyamine, or $\frac{1}{3\frac{1}{7}0}$ gr. in 60 ms. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

4. **Pilula Colocynthidis et Hyoscyami.**—12·5 p.c. of extract hyoscyamus. **B.P. Dose.—4 to 8 grs. or 0·25 to 0·5 grm.**

Pharmacology

Hyoscyamine, the principal alkaloid in hyoscyamus, is isomeric with atropine and is easily converted into the latter in the presence of a fixed alkali at the ordinary temperature. Most of the properties of hyoscyamus must therefore be identical with those of belladonna and stramonium. The following are however the chief points of difference :—(1) Hyoscyamus because of the presence of hyoscine excites the

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brain less and has a marked and rapid *sedative and soporific effect on the cerebrum.* (2) It has also more pronounced *sedative action on the spinal cord.* (3) It is also sedative to *the intestines* and is more efficacious in relieving griping and irregular contraction. (4) it is *not a powerful stimulator* of the heart. (5) It relieves *irritation of the urinary passages.* especially that of the bladder. This it does by depressing the ends of the nerves of the mucous membrane, and controlling the spasms of the muscular fibres. (6) *Intra-ocular tension* is less affected.

Therapeutics

Besides its use in those cases where belladonna is indicated, it is employed (1) to soothe cerebral excitement and produce sleep, as in mania and insomnia; (2) to lessen cardiac asthma; (3) to correct the painful griping of purgatives; (4) to relieve vesical spasm in cystitis, prostatitis, calculus, etc., often in combination with other urinary sedatives as buchu, and the alkalies; and (5) to relieve cough, as in bronchitis.

Children can bear very large doses, while the old and the weak cannot.

HYOSCINAE HYDROBROMIDUM

Hyoscine Hydrobromide. $C_{17}H_{21}O_4N,HBr,3H_2O$

Syn.—Scopolamine Hydrobromide.

Source.—The hydrobromide of an alkaloid, *l*-hyoscine (*l*-scopolamine); obtained from various solanaceous plants.

Characters.—In colourless, transparent crystals, permanent in the air and soluble 1 in 4 of water.

B.P. Dose.—$\frac{1}{200}$ to $\frac{1}{100}$ **gr. or 0·0003 to 0·0006 grm.**

Official Preparation

1. **Oculentum Hyoscinæ.**—Contains 0·125 p.c. hyoscine hydrobromide.

Pharmacology and Therapeutics

Hyoscine paralyses the parasympathetic nerve-endings like atropine, but its effects are more rapid and powerful though of brief duration. Like atropine it *paralyses the vagus endings* in the heart, but this effect is not elicited in therapeutic doses and the pulse rate is not altered. It allays pain, dilates the pupil, and checks secretion. A solution of 1 in 500 will act as a mydriatic and paralyse accommodation but unlike atropine the effect is more rapid and passes off within 3 to 5 days. The oculentum, or a 0·2 p.c. solution is used as a mydriatic in preference to atropine.

On the central nervous system it acts as a **narcotic** and has a sedative action on the convolutions **producing sleep**

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which lasts for 5 to 8 hours, and since the patient remains quiet for several hours afterwards it is largely employed as a narcotic in mania, insanity, delirium tremens, tetanus, etc. It is also used in **chorea** and **paralysis agitans** in which conditions it reduces the movements and tremors ; and relieves the rigidity and muscular hypertonus in **post encephalitic Parkinsonism** ($\frac{1}{150}$ gr. a day increased to $\frac{1}{50}$ gr. or more). Here it also reduces salivation and ocular crises. Because it reduces salivation and produces dryness of the mouth it should be given after meals. Its disadvantage is its toxcity, the margin of safety between the therapeutic and lethal dose being small.

Large doses do not necessarily produce more profound sleep, but give rise to delirium and excitement like atropine. Its use is not without danger for it depresses the respiratory and vaso-motor centres, and several cases of collapse following its use are on record. The commercial specimens vary much in purity.

A combination of scopolamine and morphine is sometimes used for the production of **general anæsthesia**. Scopolamine hydrobromide $\frac{1}{200}$ gr. and $\frac{1}{2}$ gr. of a morphine salt is injected on the night previous to the operation, and a similar or larger dose in the morning before the operation. This usually produces deep sleep and the patients do not wake till some hours after the operation, thus escaping the most painful period. Smaller doses may be given to produce **basal narcosis** prior to the use of volatile anæsthetics (*see* page 161). Scopolamine-morphine anæsthesia, "twilight sleep," is now advocated during the second stage of labour in place of chloroform (Hyoscine hydrobromide $\frac{1}{150}$ gr. with morphine sulph. $\frac{1}{6}$ to $\frac{1}{4}$ gr.). Occasionally however it causes cessation of uterine contractions and has a tendency to prolong labour, and the child may be born apnœic. Twilight sleep sometimes makes the patient maniacal, at least temporarily.

Bulbocapnine.—$C_{19}H_{19}O_4N$. One of the alkaloids obtained from the tubers of *Dicentra canadensis* and *Corydalis tuberosa*. Insoluble in water but soluble in alcohol.

Dose.—0.1 grm. or 1½ grs. by mouth in the form of tablets or subcutaneously. It is a powerful depressant to the cerebral psychomotor and motor cortex and has been introduced for the relief of various forms of tremors associated with *chorea, multiple sclerosis, paralysis agitans* and *encephalitis.*

Harmine. *Syn.—Banisterine.*—An alkaloid obtained from *Peganum Harmala.* The *hydrochloride* is generally used in *doses* of $\frac{1}{3}$ to $\frac{3}{5}$ gr. or 0.02 to 0.04 grm.

It is largely used in the treatment of **post-encephalitic Parkinsonism** either alone or in combination with hyoscine. It diminishes rigidity and tremors together with salivation and improves voluntary movements. Its effects are transient although its prolonged administration is not followed by any unpleasant by-effects. It may be administered by the mouth or as an injection.

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STRAMONIUM

Stramonium

Source.—Dried leaves and flowering tops of *Datura Stramonium*. Contains not less than 0.25 p.c. of the alkaloids of stramonium, calculated as *hyoscyamine*, or $_1\frac{1}{2}\overline{0}$ gr. in 3 grs.

Characters.—Greyish-green, ovate, petiolate, 8 to 25 cm. long, unequal at the base, with dentate margin and acuminate apex. Taste, saline and bitter. The leaves are minutely wrinkled.

Composition.—Contains *hyoscyamine*, *atropine* and *hyoscine*. *Daturine* is probably a mixture of atropine and hyoscyamine.

B.P. Dose.—$\frac{1}{2}$ to 3 grs. or 0·03 to 0·2 grm.

Official Preparation

1. **Tinctura Stramonii.**—Contains 0.025 p.c. w/v of hyoscyamine, or $_1\frac{1}{2}\overline{0}$ gr. in 30 ms. **B.P. Dose.—5 to 30 ms. or 0·3 to 2 mils.**

Pharmacology and Therapeutics

Internally.—Its action resembles that of belladonna, but it has a much more powerful effect in relaxing the muscular coat of the bronchial tubes, and it may cause irregularity of the heart's action. It is rarely used except for the relief of the paroxysms of **asthma**, for which purpose it may be smoked as cigarettes or the fumes may be inhaled, or it may be given internally. When combined with potassium nitrate, lobelia, black tea and oil of anise it resembles the well-known *Himrod's*, *Bliss's* and *Green Mountain Cure* (*see* page 78). Cannabis Indica is also an excellent adjuvant.

Like atropine and hyoscine, stramonium also relaxes the increased muscle tone of the Parkinsonian. It may be prescribed either in the form of the tincture in doses of 10 ms. up to a drachm or more three times daily, or the dry extract may be used in the form of a pill in 1 to 2 gr. doses.

Toxicology.—Poisoning by stramonium is fairly common in England, and the seeds of *Datura alba* and *fastuosa* are largely used by the *road poisoners in India*, who mix them with food, or give them to their victim to smoke, with the object of robbery.

The *symptoms* are dryness of the throat, giddiness, flushing of the face, dilatation of the pupils, and a peculiar form of dilirium associated with ludicrous movements followed by coma which may end in death.

Treatment.—Emetics, stomach-pump, stimulants, cold affusion, artificial respiration. If much delirium, give opium, but opium is less useful in these cases than atropine in opium poisoning.

Brunton recommends the cautious use of physostigmine, and Ringer advises pilocarpine nitrate in $\frac{1}{4}$ to $\frac{1}{2}$ grain doses.

Class D : Drugs acting on the Motor Nerve-endings and the Ganglia

CURARA

(*Not official*)

Syn.—Urari, Ourari, Woorara, Woorali.

Source.—The South American arrow-poison, prepared from the bark and sapwood of *Strychnos toxifera*:

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Composition.—The active principle is *curarina* or *curarine*, a most powerful poison. It exists as a brown powder, or deliquescent prisms, with an intensely bitter taste, soluble in water and alcohol, the latter solution being slightly fluorescent, is not alkaline in reaction and forms no true salts.

Dose.—1/20 to 1/2 gr. or 0.003 to 0.03 G. hypodermically.

Non-official Preparation

1. **Injectio Curaræ Hypodermica.**—10 p.c. *Dose.*—1 to 6 ms. or 0·06 to 0.4 mil.

Pharmacology

Nervous system.—It paralyses the motor nerve-endings throughout the whole body whenever a sufficient quantity enters the blood stream. In large doses it paralyses the nerve-cells. The sensory nerves are unaffected by curare.

Curare, as a rule, *only produces its physiological effect if given hypodermically*, and when taken into the stomach soon after food no results are observed. This is due to the fact that it is excreted by the kidneys more quickly than it is absorbed from the stomach and that when digested with gastric juice its toxicity is diminished.

Therapeutics

Curare is chiefly used in the physiological laboratory, but is also one of the most valuable drugs we possess for the treatment of **tetanus**, in which disease an adult can take as much as 4 grains in the 24 hours by hypodermic injection without ill-results occurring therefrom. It has been recommended as a palliative in **hydrophobia**.

CONII FOLIA

(Not official)

Syn.—Hemlock Leaves.

Source.—The fresh leaves and young branches of *Conium maculatum*, collected when the fruit begins to form.

Composition.—(1) *Coniine.* (2) *Methylconine,* (3) *Conhydrine,* (4) *Conic Acid.*

Non-official Preparation

1. **Unguentum Conii.** *Syn.—Hemlock Ointment.*—Extract of conium 7 p.c. in glycerin and simple ointment.

Action and Uses

Applied to the mucous surface conium depresses the sensory and motor endings, particularly the former. The ointment was formerly used to relieve itching of pruritus ani and the pain and spasm of hæmorrhoids.

It paralyses the motor nerve-endings similar to curara producing ascending motor paralysis. It also paralyses the sympathetic ganglia after a brief stimulation. The inhibitory ganglia of the vagus in the heart are also paralysed after slight stimulation so that the heart is first slowed and then accelerated. Death takes place from respiratory failure while the heart still beats.

It dilates the pupil, impairs accommodation and causes ptosis from paralysis of the endings of the 3rd nerve.

GELSEMII RADIX

Gelsemium Root. *(Not official)*

Source.—The dried rhizome and root of *Gelsemium nitidum*, the Yellow Jasmine.

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Characters.—Cylindrical, about 15 cm. long, 6 to 18 mm. thick, brown or dark brownish-violet, with fibrous roots occasionally attached. Roots tortuous, finely wrinkled. Odour aromatic, Taste, bitter.

Composition.—(1) *Gelsemine*, a crystalline alkaloid. (2) *Gelseminine*, mixture of alkaloids, and *gelsemic acid*; fats, resins, oils.

NON-OFFICIAL PREPARATION

1. **Tinctura Gelsemii.**—1 in 10. *Dose.*—5 to 15 ms. or 0·3 to 1 mil.

ACTION AND USES

The symptoms of poisoning are more or less the same as observed after conium, *viz.* diplopia, ptosis, dilatation of the pupil, staggering gait and sleepiness, and finally arrest of respiration.

The heart is depressed in toxic doses with fall of blood-pressure from its action on the vagal ganglia. Its effects on the nervous system are the same as observed in conium poisoning except that gelsemine is more depressant. It paralyses the nerve centres first and the endings only after large doses. It causes paralysis of all the muscles of the body by depressing the cells of the anterior cornua of the cord. The motor nerve-endings are affected after large doses.

The tincture is used in neuralgia and migraine, specially neuralgia of the fifth nerve. It may be used alone or better with butyl-chloral hydrate.

SPARTEINAE SULPHAS

(Not official)

A salt of an alkaloid derived from *Scoparii cacumina*, broom tops. In colourless, odourless crystals with a saline bitter taste. Soluble, 2 in 1 of water. *Dose.*—1 to 2 grs. or 0.06 to 0.12 grm.

ACTION AND USES

Sparteine resembles coniine in its action. It has little effect on the central nervous system. Large doses paralyse sympathetic ganglia and the motor nerve-endings. The heart is slowed and weakened from stimulation of the vagus and at one time it was used in place of digitalis, but in view of the above facts its use as a cardiac stimulant has been given up. It is however less poisonous than conium.

CLASS E: Drugs Depressing the Sensory Nerve-endings

Local anæsthesia may be produced by various means. Cold, applied either in the form of ice, or produced by spraying some volatile substance like ether or ethyl chloride, will produce anæsthesia in a localised area. Since this effect lasts only for a few seconds, cold can only be utilised for minor operations, as for instance in opening an abscess cavity or for inserting an exploratory needle, etc. Lasting anæsthesia by this method is not possible as prolonged freezing destroys the tissues. Partial anæsthesia is also produced by rendering the part anæmic, as by the application of Esmarck's bandage, or by the use of adrenaline as often done with cocaine. Drugs depressing the periphery of the sensory nerves may produce local anæsthesia by lessening the tactile sensibility of a surface to which they are applied. The most important method of producing local anæsthesia is by the use of certain drugs, specially cocaine and its derivatives, phenol, urea quinine, hydrocyanic acid dilute, etc.

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An ideal anæsthetic should produce paralysis of the sensory nerves or nerve-endings only temporarily, and in concentrations much lower than what will cause destruction of tissues.

With the introduction of many different preparations and with the advance of our knowledge, local anæsthetics are now extensively used for many operations which were formerly performed under general anæsthetics. In fact certain operations are now performed under local anæsthetics in preference to chloroform and ether. The different methods adopted for the production of local anæsthesia are as follows :—

1. Subcutaneous injection.
2. Intraspinal anæsthesia.
3. Infiltration anæsthesia.
4. Regional anæsthesia.

These will be discussed more fully under cocaine.

Local anodynes act only when pain is present. They relieve pain either by directly paralysing the nerve-endings or by central effect. They are aconite, belladonna, veratrine, phenol, chloretone, menthol, acid hydrocyanic dilute, creosote, alcohol, ether, chloroform, opium, etc.

COCAINA

Cocaine. $C_{17}H_{21}NO_4$

Source.—It is *methylbenzoylecgonine.* Obtained from the leaves of *Erythroxylum Coca*, and other species of *Erythroxylum*, or by synthesis from ecgonine.

Characters.—Colourless crystals; odourless, with a bitter taste, followed by tingling and numbness. Almost *insoluble* in water, soluble in 10 parts of alcohol (90 p.c.), in 4 parts of ether, 24 parts of olive oil and in 120 parts of liquid paraffin.

B.P. Dose.—$\frac{1}{8}$ to $\frac{1}{4}$ gr. or 0·008 to 0·016 grm.

COCAINAE HYDROCHLORIDUM

Cocaine Hydrochloride. $C_{17}H_{21}NO_4,HCl$

Source.—The hydrochloride of the alkaloid cocaine.

Characters.—In colourless, transparent crystals; odourless; taste, bitter. *Solubility.*—2 in 1 of water, 1 in 3 of alcohol (90 p.c.).

B.P. Dose.—$\frac{1}{8}$ to $\frac{1}{4}$ gr. or 0·008 to 0·016 grm.

Official Preparations

1. **Oculentum Cocainæ.**—Cocaine hydrochloride 0·25 p.c.
2. **Lamella Cocainæ.**—$\frac{1}{60}$ gr. (1.3 mgrm.) in each.
3. **Trochiscus Krameriæ et Cocainæ.**—$\frac{1}{20}$ gr. (0.003 grm.) of cocaine in each.

AMYLOCAINAE HYDROCHLORIDUM

Amylocaine Hydrochloride

Syn.—"Stovaine."

Source.—May be prepared by the action of magnesium ethyl bromide on dimethylaminoacetone.

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Characters.—Colourless, crystalline powder; taste, bitter, followed by transient insensibility of the tongue. *Soluble* in 2 parts of water, and in 3 parts of dehydrated alcohol.

B.P. Dose.—By mouth and subcutaneously.—$\frac{1}{3}$ to $\frac{3}{4}$ gr. or 0.02 to 0.05 grm. By intrathecal injection.—$\frac{1}{3}$ to $1\frac{1}{2}$ grs. or 0·02 to 0·1 grm.

BENZOCAINA

Benzocaine

Syn.—"Anæsthesine"; Ethyl Aminobenzoate.

Source—May be prepared by the reduction of ethyl *p*-nitrobenzoate.

Characters.—A white, crystalline powder; odourless; taste, slightly bitter, followed by a sensation of numbness. *Soluble* in 2500 parts of water, in 8 parts of alcohol (90 p.c.).

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

ORTHOCAINA

Orthocaine

Syn—"Orthoform."

Source.—Prepared by esterifying with methyl alcohol the reduction product of 3-nitro-4-hydroxy-benzoic acid.

Characters.—A white, or faintly yellow, crystalline powder; no odour or taste. Sparingly *soluble* in water; soluble in 7 parts of alcohol (90 p.c.), in 50 parts of ether, readily in solution of caustic soda.

B.P. Dose.—$1\frac{1}{2}$ to 3 grs. or 0·1 to 0·2 grm.

PROCAINAE HYDROCHLORIDUM

Procaine Hydrochloride

Syn.—Ethocaine Hydrochloride; "Novocaine." "Kerocaine."

Source.—By the interaction of chloroethyldiethylamine and sodium *p*-aminobenzoate.

Characters.—Colourless, crystalline powder; odourless; taste, weakly bitter, followed by a transient numbness of the tongue. Stable in air. *Soluble* in 1 part of water, and in 8 of alcohol (90 p.c.).

B.P. Dose.—$\frac{1}{2}$ to 2 grs. or 0·03 to 0.12 grm.; subcutaneously up to 1 grm. or 15 grs.; intrathecally up to 0·15 grm. or $2\frac{1}{2}$ grs.

Non-official Preparations and Derivatives of Cocaine

1. **Inj. Novocainæ et Adrenalin, R.O.H.**—Novocaine 8 grs. (2 p.c.), adrenaline solution 2 dr., sterile water to 1 oz. *Dose.*—Up to 1 dr. of the 2 p.c.

2. **Eucaine Hydrochloride, U.S.P.** *Syn.—Eucaine; Betaeucaine Hydrochloride.*—In small white opaque crystalline powder, soluble about 1 in 30 of water. *Dose.*—$\frac{1}{8}$ to $\frac{1}{2}$ gr. or 0·008 to 0·03 grm.

3. **Tropacocaine.** *Syn—Benzoyl-pseudo-tropine.*—Obtained from Java cocoa. Is alleged to be safer, more rapid, and less irritating to the eye, without dilating the pupil. Its **Hydrochloride** is freely soluble in water. Very costly. Used in 5 p.c. solution.

4. **Alypin.** *Syn.—Amydricaine Hydrochloride; Benzoyl-tetramethyl-diamino-ethyl-dimethyl-carbinol-hydrochloride.*—A white crystalline powder, readily soluble in water, giving solution of a neural reaction. A *local anæsthetic*, used hypodermically for minor operations and in ophthalmic practice. It is equal in intensity and toxicity to cocaine. May be used in strengths of from 1 to 4 p.c. *Dose*—$\frac{1}{20}$ to $\frac{1}{2}$ gr. or 0·003 to 0·03 G.

5. **Apothesine.**—*Diethyl-Amino-Propyl Cinnamate Hydrochlor.*—An anæsthetic with more profound and persistent action than cocaine, though less toxic Given

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in combination with adrenaline. For *injection anæsthesia* 1 to 2 p.c. solution, with adrenaline 1 in 100,000. *Spinal anæsthesia* 2 c.c. of 4 p.c. solution. It is relatively safe.

6. **Butyn.**—A procaine derivative containing *butyl* in place of *ethyl* and *propanol* in place of *ethanol*. A white amorphous powder, freely soluble in water. Toxicity almost equal to cocaine but acts more powerfully and the effects last longer. *Dose.*—Hypodermically, 1 c.c. or more of ½ or more p.c. solution.

7. **Borocaine.** *Syn.—Ethocaine Borate.*—A white crystalline powder. Neither toxic nor irritant. Being a salt of weak acid, in solution yields free alkaloidal base by hydrolysis. *Dose.*—⅓ to 1½ grs. or 0.02 to 0.1 grm.

8. **Benzamine Lactate.** *Syn.—Eucainæ Lactas.*—A white, crystalline powder, soluble in 5 parts of water, and in 8 parts of alcohol (90 p.c.). *Dose*—⅛ to ½ gr or 0.008 to 0.03 G.

9. **Spinocain.**—Contains novocaine, 0.2 G; strychnine sulph. 2.2 mg.; in 14½ p.c. alcohol in normal saline 2 c.c. Also contains Gliadin which prevents diffusion in the subarachnoid space until the anæsthetic has been absorbed.

PHARMACOLOGY

Cocaine is a *general protoplasmic poison*, causing irritation and destruction of cells. It stops movements of leucocytes, amœbæ and ciliated cells. A 5 p.c. solution given subcutaneously may cause death of the tissues, producing either necrosis or a sterile abscess. For the same reason its application to the eye may result in cloudiness or ulceration of the cornea, but this is not ordinarily observed.

Locally.—Cocaine hydrochloride is the strongest and the most soluble of all preparations. It has no action on the unbroken skin, although a ten per cent. ointment may produce a demonstrable depression of sensation, but no true local anæsthesia (Clark). Applied to the mucous membrane or injected subcutaneously it causes blanching from the constriction of the local blood vessels and stimulation of the vaso-constrictor nerve-endings, and **anæsthesia** from the paralysis of the sensory nerves. Injected subcutaneously it deadens the sensibility and reddens the part around the puncture. Since these effects are local it follows that the drug must be applied in sufficient concentration to reach the nerve supply of the part which it is desired to influence. Although the sense of pain is abolished, the sense of touch is not so readily lost, and the temperature sense is scarcely affected, if at all. If the solution is made alkaline by the addition of sodium bicarbonate its efficacy is increased 2 or 4 times, due to easier penetration of the free anæsthetic base as compared with its salts, specially when injected into nerve trunks, and probably for subdural injection and on application to mucous surfaces (Sollmann). These effects may be produced by a 5 to 10 p.c. solution in about one to four minutes, and will last from fifteen minutes to an hour. The period however depends upon the concentration of the solution used and the vascularity of the part. Its action is prolonged and intensified by the addition of adrenaline, which still further constricts the vessels and prevents its rapid removal by the circulation (*see* Adrenaline).

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Injected along the trunk of a mixed nerve it paralyses the sensory fibres and abolishes pain of the area supplied by that nerve. This method of producing anæsthesia is known as "nerve blocking" or "regional anæsthesia". Injected intrathecally by lumbar puncture it abolishes sensation below the umbilicus though the power of movement remains unimpaired. Cocaine possibly acts on the posterior nerve roots. This method of anæsthesia is adopted for the production of "intraspinal anæsthesia."

Internally. **Mouth.**—Locally applied it abolishes the sensibility and sensation of taste of the tongue, and the sensibility of the palate and fauces. It diminishes the salivary secretion.

Stomach and intestine.—In very minute doses it acts as a stomachic tonic, and in moderate doses diminishes the flow of the gastric juice, and deadens the sensation of hunger and of pain, if present. The same anæsthetic action is also noticed here, and cocaine therefore stops vomiting. In experimental works with strips of intestine, cocaine augments their movements. This effect is due to the direct action of the drug on the muscles. In large doses in checks peristaltic action.

Heart and circulation.—After a momentary slowing the heart beats faster. This effect was at one time thought to be due to paralysis of the vagus, but since the stimulation of the vagus slows the heart even in late poisoning, the acceleration must be due either to its direct action on the muscle or stimulation of the accelerator mechanism. After large doses the heart becomes weak and slow either from direct muscular depression or vagus stimulation, and death may take place from cardiac failure. In the earlier stages of poisoning the **blood-pressure rises** considerably from stimulation of the vaso-constrictor centre together with the increased rate of the heart. The pressure subsequently falls. As already noted cocaine causes constriction of vessels when locally applied, but no such effect is observed in general poisoning as it does not circulate in sufficient concentration to produce the effect as that would be fatal to heart and respiration.

Respiratory tract.—Topically applied it deadens the sensibility of the nasal mucous membrane. Given internally it first increases the respiratory movements from the stimulation of the respiratory centre but soon depresses them. During the spasms it becomes irregular and assumes a Cheyne-Stokes type. Death results from asphyxia due to respiratory failure.

Nervous system.—*Cerebrum.*—Cocaine stimulates the entire central nervous system, and in small doses it increases the higher functions of the brain, while in man there is some psychic stimulation and wakefulness (caffeine action). In

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large doses it acts like atropine producing talkativeness and cheerfulness, and a feeling of comfort and ease with the abolition of mental and bodily fatigue. For these effects coca leaves are largely used by the people of Peru and Bolivia. Often it causes sleeplessness though without much discomfort. The respiratory, vaso-motor and accelerator centres and the motor areas of the brain are stimulated, and there is a tendency to motor activity and restlessness. These effects are central, and therefore are antagonistic to opium. Larger doses induce convulsions, which are not of spinal origin, but produced by some action on some undetermined part of the hind brain. At an earlier stage the medulla is affected when the respiration is quickened with evidence of reflex excitability which in toxic doses may become so exaggerated as to cause convulsions like strychnine. Cocaine first stimulates the brain, then the midbrain and medulla, and finally the cord, the action being one of descending stimulation. In other words with small doses the symptoms arise from the brain, but as the dose is increased those from the lower part of the nervous system become manifest. This stimulation is followed by depression, first affecting the cerebrum, then the bulb and lastly the cord.

Eye.—A 4 p.c. solution dropped into the eye causes complete **anæsthesia** of the conjunctiva and cornea and partial anæsthesia of the iris, **dilatation of the pupil**, exophthalmos and vaso-constriction. It partially **impairs** the range of **accommodation** but the light reflex is not lost. The dilatation is not maximum, since atropine causes a further dilatation when applied to a cocainised eye. The oculomotor endings are not affected unless strong solutions are used when there is some impairment of accommodation. These effects have been attributed to the stimulation of the **sympathetic nerve-endings**, and as they are more quickly produced when the drug is applied topically than when taken by the mouth, they appear to be due to direct local action. On the other hand some hold that dilatation is caused by the weakening of the circular fibres of the iris, much in the same way as other unstriped muscles are affected. It slightly **lowers** the **intra-ocular tension** due to vaso-constriction, but this effect is not constant.

Metabolism is not much altered. The temperature rises in cocaine poisoning, due essentially to increased heat production from muscular excitement.

Kidneys.—It is eliminated in the urine, the quantity of which is increased *pari passu* with dilatation of the vessels of the kidneys, although at first they are contracted when the secretion is diminished.

Acute toxic action.—Acute poisoning is not infrequent. Susceptibility varies due partly to uncertainty of absorption and partly to

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rapid destruction and idiosyncrasy. Ordinary fatal dose is 18 grs., though death may take place from $\frac{1}{3}$ gr. Toxic symptoms have been produced from a hypodermic injection of $\frac{1}{4}$ gr. Waking hallucination like those in poisoning by Indian hemp, leading sometimes to mania, vertigo, occasionally dryness of the throat, respiratory and cardiac difficulty, cramps in the limbs, inability to move, and a sensation of foreign bodies, such as pebbles or worms, especially the latter moving under the skin, are characteristic. Pupils dilate and reflexes are exaggerated. After very large doses epileptiform convulsions accompanied by circulatory and respiratory depression occur. Death takes place through failure of respiratory centre.

Antidotes.—Emetics or pump, if necessary. Amyl nitrite, nitroglycerin, ammonia, strong coffee by the mouth or rectum, strychnine and ether hypodermically.

Chronic toxic action or "Cocainism."—Like coca craving, cocainomania is developed either in shaking off morphine or alcohol habit or from the temporary use of cocaine as a stimulant. Cocaine habit is rapidly increasing notwithstanding law against the sale of this drug. It is more dangerous to the health and moral than opium, and its habit increases sexual desire in both men and women, and also perverted sexual passion. It is taken with prepared *pan* in India, but as a snuff in other countries, which causes irritation of the nasal mucous membrane with perforation of the nasal septum. Disordered digestion, emaciation, giddiness, quick pulse, insomnia, dilated pupils, visual or other hallucination, amnesia and impotence are prominent symptoms. Habitues may consume up to 10 or sometimes 20 to 30 grs. Total abstinence from the drug, strong coffee, nux vomica, and other tonics, change of air, etc., remove this pernicious habit.

THERAPEUTICS

Externally.—Cocaine is chiefly used as a *local anæsthetic* in the following diseases :—

Eye.—Cocaine is largely used in ophthalmic practice as an anæsthetic during operation, for relief of pain, and as an astringent to constrict the vessels of the iris in inflammatory conditions. A 1 to 2 p.c. solution will allay pain, while a 4 p.c. solution or the official lamel dropped on the conjunctiva every three minutes 3 to 5 times, so far removes the sensibility as to enable the surgeon to perform many operations, as for example, cataract, etc., painlessly. Where iridectomy is necessary, a drop of the solution should be applied to the exposed iris immediately before making the section. Photophobia conjunctival and corneal pain are soon relieved by the same collyrium. Combined with atropine sulphate cocaine has been found very efficacious in **iritis** and in many painful inflammatory affections of the cornea. By adding $\frac{1}{2}$ gr. of pilocarpine nitrate to 1 dr. of a 4 p.c. solution, we can anæsthetise the eye without affecting the accommodation.

Nose, ear, anus, vagina, etc.—A 5 to 10 p.c. solution removes the sensibility of the mucous membrane of the nose, internal meatus of the ear, vagina, os uteri, urethra and rectum, so as to allow small operations to be performed painlessly. The nasal irritation in hay fever, anal and labial

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pruritus, earache, and the pain of anal fissure or ulcer are all relieved by the local application of cocaine.

Skin.—Although cocaine is known not to be absorbed by the intact skin, yet the application of the alkaloid combined with lard or oil allays the burning and pain of eczema, erysipelas, urticaria, sore nipples, etc. The pain and irritation of **burns** and **scalds** are soon relieved, if the part is first brushed over with a 4 p.c. aqueous solution of cocaine hydrochloride and then the pure alkaloid combined either with carron oil or with paraffin or boric acid ointment is applied. A hypodermic injection of cocaine removes the pain of scorpion-stings. Buboes, small tumours, inflamed bursæ and small abscesses may be painlessly dealt with after injection of cocaine in their neighbourhood. Many superficial **neuralgias** may be relieved by the local application of the alkaloid in oil of cloves, and sciatica by the injection of an aqueous solution into the sheath of the nerve.

Intraspinal anæsthesia.—Intraspinal anæsthesia by means of cocaine solution, introduced by lumbar puncture, was advocated for the performance of certain minor operations, and 1 c.c. of a 2 p.c. solution was injected into the subdural space after withdrawing an equal amount of cerebro-spinal fluid. It was soon recognised as being too dangerous and its use was given up till Professor Jonnescu introduced stovaine (amylocaine hydrochloride) and reported a remarkable series of cases of its successful use. To these solutions he added strychnine which rendered the anæsthetic solution more tolerable to higher nerve centres. The dose recommended by him produced complete paralysis of the posterior sensory roots. For injection into the lumbar regions the following doses have been recommended by Jonnescu, viz.—stovaine, 0·002 grm. ($\frac{1}{30}$ gr.) with strychnine hydrochloride 0·001-0·002 grm. ($\frac{1}{60}$ to $\frac{1}{30}$ gr.). For cervical and dorsal regions 0·005-0·02 grm. ($\frac{1}{12}$ to $\frac{1}{3}$ gr.) and 0·0005-0·001 grm. ($\frac{1}{100}$ to $\frac{1}{60}$ gr.) respectively.

Sterilised solutions of stovaine are supplied in ampoules ready for use, and is put up in two forms. The *heavy solution* contains 5 p.c. of stovaine combined with glucose, each ampoule holding 2 c.c. When introduced into the thecal canal, the solution, owing to its specific gravity, assumes a position which can be varied by tilting the patient's spine, thus adjusting the level of the analgesia to some extent. To prevent the anæsthetic solution reaching the higher nerve centres, or from acting on the root of the phrenic or other respiratory nerves, the head and the shoulders must be kept at a higher level raised on pillows. Since the drug gets fixed in about 10 minutes the position may be altered after this period. The *light solution* is a 10 p.c. solution and is put up in ampoules of 1 c.c. in normal saline. It has the same specific gravity as the cerebro-spinal fluid, and is

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unaffected by gravitation. With this solution the patient may at once be placed on Trendelenburg position, whereas with the heavy solution it can only be done after the drug gets fixed in the tissues, i.e. after ten minutes which implies some waste of time.

Besides stovaine, novocaine and tropacocaine have also been used for the production of spinal anæsthesia. But all these drugs have the drawback of being effective only in fairly concentrated solution and spreading towards the head by gravitational diffusion when a Trendelenburg position is adopted during operation necessary to maintain blood-pressure. The introduction of percaine has altered the position. Although highly toxic it can be used in very high dilutions. Ampoules containing 20 c.c. of 1 in 1500 solution in 0·5 p.c. saline ready for use are available. As the solution is lighter than the cerebrospinal fluid, the patient should lie on his face with his buttocks slightly raised for at least five minutes. This enables the solution to reach the posterior nerve roots. An injection of ephedrine or adrenaline is given at the same time to combat any fall of blood-pressure.

Spinal anæsthesia should be confined to operations not extending above the umbilicus. It is an ideal method for gynæcological operations, and for operations upon the rectum and bladder, and in diabetics. It is specially useful for persons who have a dread for chloroform or ether, or for losing consciousness. Since it blocks the nervous paths of shock impulses, it is an ideal anæsthetic for cases where shock from operation is anticipated, but should be avoided where the nervous shock is already present.

A frequent complication is retching and vomiting which makes abdominal operation rather disturbing. Failure of respiration sometimes gives rise to grave anxiety. This is due to direct action on the centre and should be treated with oxygen, or oxygen and CO_2 5 p.c. Some fall of blood-pressure is always present and this is not of any consequence.

Injection into the nerve sheath (intraneural) is used when a permanent effect is desired as into the cut nerves in amputation stumps.

Anæsthesia by the local infiltration method consists in subcutaneous injection of either 0·1 p.c. of cocaine or 0·24 p.c. of eucaine with 0·8 p.c. of sodium chloride, along the proposed lines of incision, and then into the deeper parts before cutting them. Nowadays cocaine is rarely used for the purpose, as it produces toxic symptoms, and novocaine is widely used, which in suitable doses is free from any toxicity, moreover the solution can be sterilised by boiling. As it does not constrict the arterioles, a little adrenaline chloride solution (0·002 to 0·005 p.c.) is added to check hæmorrhage, to prolong the period of anæsthesia and to reduce toxicity. The strength of the solution is 0·25 to 1 p.c. and the usual

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procedure is to start by raising on the skin over the required area a number of wheals by injecting the solution endermically. After a number of these wheals have been formed insert the needle deep into the tissues. In this way quite a large area can be made anæsthetic, and if necessary can be extended to deeper tissues by subsequent injections.

In the **regional anæsthesia** the anæsthetic is used to block the passage of pain impulses by exposing the sensory nerve trunks to the anæsthetic solution while leaving the nerve endings unchanged so that sensation of pain does not reach the central nervous system. In the infiltration anæsthesia, the actual nerve-endings of the part to be operated upon are anæsthetised.

Regional anæsthesia has been largely used, and with much success, in gastric surgery by blocking the greater and lesser splanchnic nerves by infiltrating the loose retro-peritoneal tissue around the cæliac plexus with a 5 p.c. solution of novocaine and adrenaline. By this method the stomach, small intestine, omentum, liver and hilus of the spleen can be sufficiently anæsthetised to be handled painlessly. The abdominal wall and parietal peritoneum are previously anæsthetised by the local infiltration method.

Internally. **Gums and teeth.**—Cocaine, preferably the alkaloid, as it is less likely to be washed away by the saliva, is largely employed in dentistry to deaden the sensibility of the exposed pulp. Cocaine hydrochloride 1, chloral hydrate 5, and camphor 5, form an oily liquid when warmed, which removes toothache. A tooth may be painlessly extracted by injecting a solution into the gums at its base, but this is a risky procedure. The mere rubbing of cocaine over the gums deadens their sensibility to such an extent as to annul the pain of the first application of the forceps.

Throat and larynx.—By applying a 20 p.c. solution to the soft palate and pharynx, enlarged tonsils or small growths in those parts may be excised, or the galvano-cautery applied painlessly. By the same method the larynx may be explored and minor operations performed there without spasm or pain.

In painful sore-throat cocaine and rhatany lozenges give great relief by acting locally.

Stomach.—For its local effects on the gastric mucous membrane, it may sometimes be used in **sea-sickness** and **vomiting of pregnancy.** $\frac{1}{8}$ gr. with 15 ms. of glycerin in 1 dr. of water may be given every hour for this purpose.

Toxic effects of local anæsthetics.—Quite a large number of operations are now performed with the aid of local anæsthetics, and since this entails the use of these drugs in large doses their toxic effects should be carefully noted. It should be remembered that local anæsthetics are protoplasmic poisons possessing special affinity for nerve tissue, injections of large amounts in solution will naturally affect the brain

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and the vital centres. The symptoms of overdosage are excitement, restlessness, deep and rapid breathing, dilated pupil, and feeble pulse. These are followed in severe cases by unconsciousness, convulsions and death. According to Farr intravenous lethal dose of a local anæsthetic is one-tenth of its subcutaneous lethal dose. Accidental introduction into a vein therefore is responsible for most of the cases of sudden collapse and death. Adrenaline increases the liability to cardiac failure by causing fibrillation of the ventricle as happens after chloroform anæsthesia.

In spinal anæsthesia cocaine is much too toxic and its use has been given up. Some patients have special idiosyncrasy to cocaine and death has occurred from mere application of small amount to mucous surface (Ross and Fairlie). The use of cocaine and butyn should be restricted to surface application, and the total quantity of cocaine should not exceed 1 to 1½ grs.

Novocaine is considered to be the safest. Given subcutaneously the total quantity should not exceed 0·2 grm. when used in 2 p.c. solution. It is better not to exceed a concentration of more than 1 p.c. It injures the kidney and may cause albuminuria.

After-effects.—Apart from the after-effects seen after general anæsthesia, severe headache is a common trouble and has been attributed to increased intracranial pressure. Mild cases yield to ordinary treatment. In severe forms, hypertonic saline infusion or an intravenous injection of glucose and saline (50 p.c. glucose), or 2 c.c. of 50 p.c. magnesium sulphate are useful.

Transient paralysis of the sphincters of the bladder, or squint may appear, which disappear within a few weeks.

The following are the disadvantages of using cocaine :—

1. Its general poisonous action.
2. Growth of fungus on keeping.
3. Its tendency to formation of vicious habit.
4. It is destroyed by boiling.

Benzocaine was introduced under the name of *Anæsthesine*. It is insoluble in water but fairly soluble in oil, and is largely used as a surface anæsthetic in the form of dusting powder mixed with starch or talc powder in the proportion of 10 to 15 p.c., in burns, ulcers, eczema, etc. It may also be used as an ointment (10 p.c.). As a suppository (10 gr.) it may be used in painful and inflamed piles.

Procaine hydrochloride or *Novocaine* has replaced cocaine in injection anæsthesia as it is less toxic and less irritating, but the effects are less prolonged. Since it is absorbed with difficulty from mucous surfaces it cannot reduce pain when applied to the conjunctiva, nose, or urethra. It does not constrict the vessels and therefore it is usually combined with adrenaline which makes it less toxic by diminishing

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absorption and prolongs its effects. For the production of regional or infiltration anæsthesia it is largely used in place of cocaine.

Amylocaine hydrochloride or *Stovaine* is slightly less toxic than cocaine and is preferred for intraspinal anæsthesia. It is however slightly more toxic than novocaine. It is an irritant and causes hyperæmia, does not constrict vessels nor cause dilatation of the pupils.

Orthocaine is largely used as a local anæsthetic to abraded and mucous surfaces and is used for its local effect to relieve gastric pain, in ulcers, simple or malignant, in 1 to 2 gr. doses, and as a dusting powder or as an ointment (10 p.c. in simple ointment) to relieve pain in burns, ulcers, etc. It has the drawback of producing severe irritation and even necrosis.

PERCAINE

(Not official)

Syn.—Nupercaine.—Hydrochloride of *a*-butyl oxycinohoninic acid diethylethelenediamide. In odourless, tasteless crystals, readily soluble in water forming a neutral solution.

Dose.—3/4 to 1 1/2 gr. or 0.05 to 0.1 gm.

Action and Uses

Percaine differs from the above group in being a derivative of quinoline, a group of substances not used as local anæsthetic. It is soon decomposed by the presence of a trace of alkali, and must be kept in alkali-free glass containers, and syringes, needles, etc., must be boiled in water free from any alkali and should not come in contact with tap water or Ringer's solution. The drug was introduced by Karl Meischer and since then it has profoundly modified the technique of spinal analgesia. The main characteristics are its extreme potency and duration of action. It is about twenty-five times more toxic than novocaine and three times than cocaine but this is offset by the fact that its minimal effective concentration is about one-fortieth. It is also extremely effective for surface application, and has a more prolonged action than cocaine. A dilution of 1 in 125,000 has a demonstrable effect on rabbit's cornea, whereas it requires 1 in 10,000 to produce the same effect with cocaine. Although it is largely used for spinal anæsthesia symptoms of poisoning were observed after excessive doses, viz. clonic convulsion, irregularity of the heart, circulatory failure, cyanosis and respiratory paralysis.

For *local anæsthesia* to mucous surface a 1 to 2 p.c. solution with a few drops of 1 in 1000 adrenaline is sufficient. For *infiltration anæsthesia* the strength is 0.5 to 1 in 1000, with the addition of 10 to 20 drops of 1 in 1000 adrenaline solution for every 100 c.c. of anæsthetic. For *spinal anæsthesia* a 1 in 1500 solution in 0.5 p.c. saline is used, and of this 6 to 18 c.c. are required.

Sterile solutions of 20 c.c. ampoules of 1 in 1500 in 0.5 p.c. saline are available.

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In the following table the differences in the action of cocaine, amylocaine, procaine and benzamine lactate have been summarised.

	Cocaine	Amylocaine or Stovaine	Procaine or Novocaine	Benzamine Lactate
Toxicity	Highest	2/3 of cocaine but more than procaine	Low; 1/3 to 1/7 of cocaine	1/2 of cocaine
Irritation and tissue injury	Non-irritant in ordinary concentration	Irritant; induration in high concentration	Non-irritant	Smarting pain
Vaso-constriction	Yes	Dilates vessels	Dilates vessels	Nil
With adrenaline	Prolongs effect	Interferes vaso-constriction	Vaso-constriction. Acts efficiently	Interferes its effect
Stability of solution	Slowly deteriorates. Should be freshly made	Keeps well, but destroyed by trace of alkali	Keeps well but gets discoloured	Keeps well
Sterilisation	Destroyed by boiling. Can be brought to boiling point	Can be boiled	Can be boiled	Can be boiled
Pupil	Dilates	Nil	Nil	Nil
Surface Anæsthesia	Efficient	Not efficient	Not efficient	Nil
Uses	Useful for surface anæsthesia with adrenaline.	With strychnine for spinal anæsthesia; also for infiltration anæsthesia	Useless for surface anæsthesia. Useful for spinal and infiltration anæsthesia	Useful for infiltration anæsthesia

GROUP VI

DRUGS ACTING ON THE CARDIO-VASCULAR SYSTEM

Class A: **Drugs acting on the heart**

1. Cardiac tonics
   Digitalis, Strophanthus, Squill, Apocynum
2. Cardiac depressants
   Aconite, Acid Hydrocyanic Dilute

Class B: **Drugs acting on the vessels**

1. Drugs raising the blood-pressure (Vaso-constrictors)
   Adrenaline, Ephedrine, Pituitary Extract, Ergot
2. Drugs lowering the blood-pressure
   (*a*) Vaso-dilators: **Amyl Nitrite, Nitro-glycerin, Erythrol Tetranitrate, Sodium Nitrite, Spirit of Nitrous Ether, Acetyl Choline**
   (*b*) Reducing the volume of blood: **Leech, Bloodletting**

Class A: Drugs acting on the Heart

The heart is a peculiarly constructed nervo-muscular organ performing complex functions. It is capable of originating spontaneous rhythmical movements. The theory that these movements are due to the ganglia located in the heart is no longer believed, but evidence goes to prove that they originate from the spontaneous impulses generated in the muscle itself—myogenic—and Gaskell describes as its functions, *rhythmicity, excitability, contractility, conductivity* and

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tonicity. Though the muscular fibres spontaneously contract yet they can be controlled and regulated by the nerve centres. Two centres control the cardiac mechanism, *viz.*, the cardio-inhibitor and the accelerator. Afferent impressions from various parts of the body, including the seat of mind and the heart, are transmitted to the centres in the medulla to be reflected to the heart. The vagus system consists of the centre, nerves, ganglia and nerve-endings, the chief function so far as the heart is concerned is that of restraint or inhibition. It begins at the centre whence the fibres pass to groups of cells in the heart-wall forming vagus ganglia, whence fibrils pass to the sino-auricular node (normal pace maker) in the auricle and to the bundle of His. Stimulation of any part of this system is followed by slowing or weakening of the heart-beat with depression of conductivity and loss of tone, either by acting on the auriculo-ventricular bundle or by diminishing the irritability of the ventricle itself, or tonicity; while depression results in increased frequency and strength of the beat and increased tone by making the heart free of the vagus influence. The accelerator nerves belong to the sympathetic system, and consist of centre, nerves, ganglia and nerve-endings. The effect of excitation besides increasing the rate, is to increase the force of contraction and conductivity. The vagi (parasympathetic) and accelerators (sympathetic) are therefore antagonistic in their effects, and since they are in activity they form a sensitive balanced control mechanism which favour prompt response to any influence.

The contraction of the heart is initiated in the sino-auricular node situated at the mouth of superior vena cava.

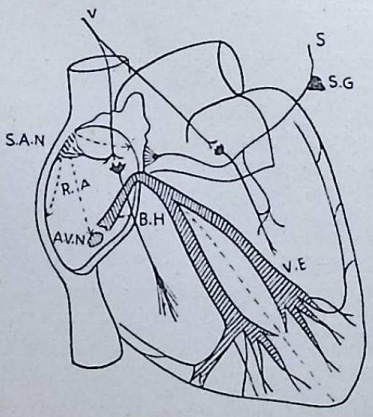

Fig. 2.—Innervation of the Heart. S.A.N., sino-auricular node. A.V.N., auriculo-ventricular node. B.H., bundle of His dividing into two branches; one entering the right, the other left ventricle. V., parasympathetic fibres (vagus) terminating round the ganglion cells in the auricles. V.E., vagus endings in the auricles and ventricles. S., sympathetic terminating round the stellate ganglion (S.G.), and the nerve fibres issuing from the ganglion end in auricles and ventricles. (Modified from Wright's Applied Physiology)

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From here the wave passes over both the auricles to the auriculo-ventricular node, which is situated between the auricles and the ventricles. From the auriculo-ventricular node the wave passes down the bundle of His to the endocardial surface of both ventricles. The bundle and its branches are composed of large fibres, which are termed Purkinje fibres.

In order that the heart may functionate properly it must have ample supply of oxygen. Under normal conditions weight for weight this oxygen consumption is greater than any other tissue of the body. It receives oxygen from the coronary arteries and the efficiency of coronary circulation depends upon the heart's contraction. As long as the supply of oxygen is adequate the heart can utilise both carbohydrate and protein to supply heat and energy, and any decrease in oxygen will enable the heart to utilise glycogen to a limited amount which it reduces to lactic acid, but is rapidly poisoned by it. Therefore any interference with coronary circulation at once injures the heart, and other things being equal slowing of the heart ensures better coronary circulation resulting in improved nutrition and recuperation. The coronary arteries are supplied by the sympathetic and the parasympathetic vagus. The stimulation of the former dilates and that of the latter constricts the vessels. It follows therefore that both the blood supply to the heart and consequently its work are diminished by vagus stimulation and increased by sympathetic stimulation.

The maintenance of efficient circulation depends upon the condition of the heart muscle. Normally the different parts of the entire circulatory system are so adjusted that they facilitate the work of the heart, and any disturbance in any part of the circulatory chain entails extra work upon the heart muscle which asserts itself to meet the requirements of the body.

Two conditions intimately associated with heart disease require special mention, *viz.* "compensation" and "auricular fibrillation."

Compensation.—The term is used to designate the degree of impairment of heart's activity, *i.e.*, the ability of the heart to maintain efficient circulation against some leakage or other adverse condition. We speak of failure of compensation or heart failure, when the heart is unable to maintain it. This inability is due to excessive strain on the heart muscle. For practical purposes Mackenzie differentiates two functions of the heart muscle. The one necessary to maintain efficient circulation when the body is at rest, which he calls "rest force," and the other called into action during an effort, however small, which he calls "reserve force." The first signs of heart failure are observed with the exhaustion of the reserve force, and if the strain continues without

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any repair or recuperation, true signs of heart failure appear, when the heart muscle is unable to maintain efficient circulation even during the period of rest. The signs of failure of compensation are dyspnœa, orthopnœa, weak and dilated heart, rapid pulse, sluggish peripheral circulation with cold extremities, œdema and dropsy.

Auricular fibrillation is a condition characterised by disordered rhythm of the heart. There is complete irregularity of the pulse—no two beats being the same in force or rhythm—and absence of signs of auricular contraction. It is a serious complication, and occurs in almost all cases of heart failure and in old standing cases of mitral disease.

Normally the wave of excitation originated at the sinus node is followed by a refractory period, and the whole auricle remains in that condition till the wave is completed. In fibrillation the refractory period is shortened and the wave of excitation becomes slow so that by the time the waves have travelled over the auricle another part recovers (owing to shorter refractory period) and sends waves of excitation before the previous ones have completed. Thus innumerable waves of excitation arise from abnormal parts of the auricle and travel round and round producing what has been termed by Lewis "circus movements." These irregular impulses pass into the ventricles which respond irregularly and inefficiently at a rate far greater than their maximum capacity. As a consequence of this the ventricular muscles become exhausted. Digitalis and quinidine are very useful in this condition.

Heart rate.—The rate of the heart may be affected in the following ways :—

A. **Slowing of the rate may be caused**

(*a*) *By acting on the vagal centre.*—Drugs which stimulate the central nervous system also stimulate the cardiac centre. But the effects on the vagal centre is more powerful than on the sympathetic, so that slowing of the heart results. The best example of stimulation of the vagal centre is deficiency of oxygen in the blood as happens in asphyxia. Aconite, digitalis, strophanthus, squill, convallaria, picrotoxin, strychnine and morphine cause slowing by stimulation of the vagal centre. High blood-pressure affects the medulla and causes slowing of the heart, and any cause which will raise the blood-pressure will produce slowing. Thus adrenaline produces slowing during the period when the pressure is highest, although it has no direct effect on the medulla. Pituitarin also acts in the same way. Afferent impulses through the 5th and the 10th nerves reflexly stimulate the vagal centre, e.g., inhalation of ammonia vapour.

(*b*) *By acting on the ganglion cells.*—Nicotine, coniine, lobeline and gelsemium stimulate the ganglion cells in the course of the vagus and cause slowing. These are depressed

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subsequently and in large doses paralysed when the rate is accelerated.

(*c*) *By acting on the nerve-endings.*—Stimulation of the endings of the parasympathetic (vagus) causes slowing of the rate; e.g. by pilocarpine, choline, physostigmine, and members of the digitalis group.

(*d*) *By acting on the muscle.*—Drugs alter the rate of the heart by their action on the muscle. Many drugs in small doses cause slowing, while in large doses produce quickening through their effects on the excito-motor portion of the heart (bundle of His). Barium, digitalis, quinidine, aconite and pituitary cause slowing by acting directly on the cardiac muscle.

B. **Quickening of the rate may be caused**

(*a*) *By acting on the sympathetic centre.*—Very little is known regarding the action of drugs on the accelerator centre. Cocaine stimulates the centre and causes acceleration of the heart. Excitement and anoxæmia increase the frequency of the heart's rate either by stimulating the sympathetic centre in the medulla or by stimulating the secretion of adrenaline.

(*b*) *By acting on the nerve-endings.*—Atropine, hyoscyamine and hyoscine cause quickening by paralysing the vagal nerve-endings, while adrenaline, tyramine, ephedrine, cocaine, and pilocarpine in small doses cause acceleration by stimulating the sympathetic nerve-endings.

(*c*) *By acting on the ganglion cells.*—Nicotine, coniine, lobeline and gelsemium cause acceleration in large doses by paralysing the ganglion cells in the course of the vagus.

(*d*) *By acting on the muscle.*—Caffeine, digitalis in poisonous doses.

1. Cardiac Tonics

DIGITALIS FOLIUM

Digitalis Leaf

Source.—Leaf of *Digitalis purpurea*, rapidly dried at a temperature between 55° and 60° as soon as possible after collection.

Characters.—From 10 to 30 cm. or more in length, up to 4 to 10 cm. broad, with a winged petiole, ovate-lanceolate, subacute, crenate. Upper surface somewhat rugose, dull green, slightly hairy. Under surface paler, pubescent, with prominent veins. No odour. Taste, very bitter.

Composition.—The chief active principles of digitalis are several *glycosides* which on hydrolysis split up into sugar and a non-sugar component, *aglucone*. They may be grouped into two classes, *viz.*:—

(*a*) *Alcohol soluble.*—

1. *Digitoxin* crystalline, $C_{41}H_{64}O_{13}$, represents the digitalis action. It is the most abundant, active and most important constituent of the leaves (0·2 to 0·4 p.c.). This exists with

2. *Gitoxin.*

3. *Digitalin* amorphous, $C_{36}H_{56}O_{14}$. Occurs in leaves and seeds. Splits into dextrose, digitaligenin and digitalose. Produces typical digitalis effect; half as active as digitoxin.

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(*b*) *Water soluble.*—

4. *Gitalin* and *digitalein* are mixtures of indefinite composition.

5. *Digitonin*, a saponin, occurs both in crystalline and amorphous forms. The crystalline form is less readily soluble in water. It helps the solution of digitoxin in water.

Official Preparations

1. **Digitalis Pulverata.** *Syn.*—*Powdered Digitalis.*—Leaf reduced to no. 20 powder, no portion being rejected. Standardised by biological assay to contain 10 units in 1 gramme. **B.P. Dose.**—½ to 1½ grs. or 0·03 to 0·1 grm. *For single dose.*—3 to 10 grs. or 0.2 to 0.6 grm. *Enters into* the preparation of tr. digitalis by method 2.

2. **Infusum Digitalis Recens.**—Freshly prepared from powdered leaf. Should be used within 12 hours of preparation. One-twentieth the strength of tincture. 6 units of activity in 4 oz. **B.P. Dose.**—90 to 300 ms. or 6 to 20 mils. *Single dose.*—1 to 4 oz. or 30 to 120 mils.

3. **Tinctura Digitalis.**—No. 1, prepared from the leaf, and No. 2, from powdered leaf. Contains 6 units of activity in 90 mils. **B.P. Dose.**—5 to 15 ms. or 0·3 to 1 mil. *For single dose.*—30 to 90 ms. or 2 to 6 mils.

Non-official Preparations

1. **Digitalin**—Under this name the following varieties are found—

(*a*) **Amorphous Digitalin** (*Homolle*).—Consists of mixture of glycosides. Insoluble in water. *Dose.*—1/60 to 1/30 gr. in granules.

(*b*) **Crystallised Digitalin** (*Nativelle*).—Consists mostly of digitoxin, in light-white needles, soluble in chloroform, insoluble in water. Is cumulative. *Dose.*—granules 1/240 and 1/600 gr. 1/600 gr.=16 ms. of tincture or 1½ gr. powdered leaf.

2. **Digitoxin** (*Merck*).—In minute white crystals. *Dose.*—1/250 to 1/61 gr.

3. **Digalen.**—A solution said to contain 0.3 mgrm. of digitoxin in 17 ms. 15 ms.= 2 grs. of leaves, or 18 ms. of tincture. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.

4. **Digipuratum.**—A purified solid extract. Contains the cardiac glycosides of the leaves in combination with tannin and freed from most of the inactive constituents. Obtainable in solution, tablets (0.1 grm.) and ampoules.

5. **Pilulæ Digitalis Co., B.P.C.** *Syn.*—*Guy's Pill.*—Powder digitalis; powder squill, pill of mercury, each 1 gr., syrup of liquid glucose q s. for one pill. *Dose.*—1 to 2 pills.

Pharmacology

Locally.—Digitalis, owing to the presence of glycosides, powerfully irritates the mucous membrane and subcutaneous tissues causing inflammation and pain. This effect is more marked with digitoxin than with digitalin which is often used subcutaneously without causing any local irritation. Subcutaneous injection of digitoxin causes much pain and irritation and sometimes a sterile abscess.

Internally. **Gastro-intestinal tract.**—Small doses appear to have no action, but the glycosides and the saponins are sometimes irritating to the gastric mucous membrane. If continued long even in therapeutic doses it causes **nausea** and **vomiting,** due not to any local irritant effect on the stomach but to stimulation of the vomiting centre after absorption, or perhaps through stimulation of the sensory fibres of the vagus in the heart, which is a secondary manifestation of the cardiac action. In practice this should be

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regarded as a sign of over-digitalization. It is slowly absorbed from the intestine, and is not affected by the digestive juices, but in case of venous engorgement, as happens in diseases of the heart, absorption is delayed and there is some destruction of the glycoside. The tincture and digitoxin however are quite easily absorbed and will manifest their effect on the heart in from four to seven hours. According to Cloetta, digitoxin is more resistant to digestive juices than other glycosides. All the glycosides are readily absorbed when given per rectum.

Heart and circulation.—Digitalis produces its principal effects on the circulatory system. It **slows the rate of the heart, prolongs the period of diastole, increases the force of contraction,** and **improves the tone of the muscle.** Before proceeding to describe its action on the different structures of the heart it will be convenient to discuss its effects on the frog first, for it was in this animal that its effects on the heart were first studied. Although the effect of digitalis on the frog's heart is different to that on the mammalian heart it has been pointed out that the reaction of human heart in diseased condition approximates more closely to that of the frog's heart than to that of the mammalian organ (Cushny).

Frog.—If a tracing of the heart of a decerebrated frog is taken and then an injection of digitoxin is given, a well-defined series of phenomena are observed. The systole becomes more powerful and the heart becomes slower from prolongation of the diastole. The increased contraction enables the heart to empty itself more completely during the systole and the ventricles become more completely filled through prolonged diastole. If the dose is increased the auriculo-ventricular conductivity is lowered and the rhythm is altered. There may be two or more beats of the auricle for each ventricular contraction, or there may be a long pause in diastole between a series of regular contractions. Finally, the ventricles may stop beating and remain standstill in the position of systole whilst the auricle continues to beat. It is obvious that two changes take place in the frog's heart, *viz.* (1) *change in rhythm*, and (2) *change in tone and contraction*. These effects are due to direct action of the drug on the cardiac muscle since the same effects can be elicited after destruction of the central nervous system, or division of the vago-sympathetic fibres, or in the excised heart under atropine.

Mammals.—The action of digitalis on the mammalian heart may be divided into three stages depending on the preponderance of its effects either on the inhibitory mechanism or on the cardiac muscle.

The first or therapeutic stage is characterised by moderate slowing through stimulation of the vagus centre and

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increased contraction of the cardiac muscle resulting in more complete systole. The output of the heart is thus increased while the slowing gives more time for the ventricles to be better filled. As a result of this effect the veins empty themselves more thoroughly into the heart, the venous pressure falls and the arteries get better filled. The arterial pressure first rises owing to the increased ventricular force and greater output. If the dose is increased the arterioles contract from stimulation of the vaso-constrictor centre and from direct stimulation of the muscles of the vessels.

The second stage or that of poisoning is marked by over-activity of the inhibitory mechanism and the pulse becomes slower and irregular. The heart gets more time to fill, consequently the output with each systole is greater than normal. But since the rate is extremely slowed the total output per minute and the efficiency of the pumping action of the heart is less than normal. Moreover owing to the inhibition of the conductivity of the muscles of the auriculo-ventricular bundle, the auricular impulses do not pass on to the ventricles, thus producing incipient or less frequently complete heart-block, *i.e.*, the ventricles beat at a slower rate than the auricles, so that the number of beats of the heart and that of the pulse is different.

The third stage follows excessive doses and is hardly ever observed clinically in man. The heart muscle becomes extremely irritable and the ventricular rhythm becomes accelerated, but the nervous mechanism is not involved since the stimulation of the vagus may slow the rate. The auricular muscles are also affected and the combination of these effects gives rise to irregularity of the heart producing auricular-ventricular arrhythmia, spontaneous rhythm, extra-systole and finally fibrillation leading to failure of myocardium and the stoppage of the heart in diastole.

Digitalis produces all the above circulatory effects through its action on the following five structures :—

1. The sinus node.
2. The cardiac muscle.
3. The auriculo-ventricular bundle.
4. The coronary arteries.
5. The systemic arteries.

1. By its inhibitory action on the **sinus node** it causes a **slowing in the rate of the heart.** This effect may not be due entirely to digitalis action on the sinus node, but in part to stimulation of the vagus centre. This slowing is often a desirable therapeutic effect, but in certain conditions, *viz.*, old age, cardio-sclerosis, and in some infectious fevers, therapeutic doses of digitalis fail to effect any such slowing. A second effect of digitalis on this node is to interfere with the regular rhythmic projection of impulses, so that a **sinus arrhythmia** is set up, *i.e.*, the heart-rate shows regular

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alternating short phases of acceleration and slowing. This effect is also due to stimulation of the vagus, and is checked by atropine or section of the vagi.

2. Digitalis acts directly on the **cardiac muscle**, and its effect here is threefold, *viz.*—(1) it increases its **tonicity**, *i.e.*, maintains a state of tone, which keeps it in readiness to respond at once to stimulation; (2) it increases its **contractility**; and (3) it renders it more **irritable**, *i.e.*, increases its sensitiveness to stimuli. The papillary muscles are also toned and strengthened. The first two effects—increase of tone and contractility—are of great value in all cases of cardiac failure, but the third effect—*irritability*—if increased beyond the normal, may give rise to harmful symptoms, such as premature contractions, tachycardia, and fibrillation.

In therapeutic doses the rhythm of the heart becomes slower, the ventricles contract and become smaller and empty themselves more thoroughly than they normally do, so that with each beat the ventricles expel more blood into the aorta and pulmonary artery. The ventricular changes under digitalis consist in reducing the number of beats and increasing the relaxation of the fibres from inhibitory activity, and strengthening the systole from direct action on the muscle, which also limits the period of relaxation without affecting the rhythm.

3. The function of the **auriculo-ventricular bundle** is to conduct impulses from the auricle to the ventricle, so that the ventricular contraction follows the auricular one regularly, and the time taken for the passage of the impulse down this bundle (A-V interval) is one-fifth of a second. Digitalis may cause, through interference with this conduction, (1) a prolongation of the A-V interval, or (2) in toxic doses may lead to **incipient**, or even less frequently to **complete heart-block.** These effects, the first of which can only be ascertained by tracings, are toxic, and call for the stoppage of the drug. On the other hand this prolongation of the auriculo-ventricular interval makes it useful in the treatment of auricular fibrillation, so that digitalis blocks many of the auricular impulses to pass into the ventricle.

4. In therapeutic doses it is doubtful if digitalis has any constricting effect on the **coronary arteries.** The increased aortic pressure, the prolonged diastole, and the greater contraction in systole resulting from therapeutic doses of digitalis, lead to a vastly improved coronary circulation, with the result that the nourishment of the heart-muscle is improved. In toxic doses, however, *coronary constriction* does occur, and this may cause such muscular weakness that the condition known as **pulsus alternans** may arise.

5. Small doses of digitalis have no direct action on the blood vessels, but toxic doses cause **constriction of the arteries**, partly by action through the vaso-constrictor centre and partly by direct action on the muscle walls. The heart

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muscle being more sensitive to digitalis than the arterial walls, the amount of digitalis which produces a definite effect on the vessel is fatal to the heart, and the consensus of opinion among modern workers on the circulation is that *in therapeutic doses digitalis does not cause any arterial constriction and does not raise the general blood-pressure.*

Temperature.—In medicinal doses it has no influence on the temperature, but in toxic doses it reduces it even in health. The effect is possibly due to increased activity of the heat controlling centre (Cushny).

Nervous system.—In medicinal doses it has no influence on the brain, the cord, and the sensory and motor nerves. In large doses it causes giddiness, headache, dimness of sight and disturbed hearing. Flashes of light, and a blue halo around bright objects also appear before the eyes. All these symptoms are probably due to some disturbance in the cerebral circulation. The reflex excitability and motor nerves are depressed only by toxic doses.

Kidney.—Digitalis is a powerful **diuretic** in cardiac dropsies, and the effect is proportional to the improvement in circulation. In dropsies not due to circulatory failure, it has little or no effect. Since it produces no diuresis in healthy individuals the diuresis cannot be due to any action on the kidneys. According to Sollmann the following factors improve renal circulation, *viz.*—(*a*) relief of venous pressure, (*b*) increased output of the heart, and (*c*) the hydræmia resulting from the absorption. If large doses are administered, the vaso-constriction may be so great as to stop the excretion altogether. It takes about 48 hours to produce any diuretic effect after commencing the treatment with digitalis.

It has no action on the composition of the urine.

Uterus.—The muscular fibres are supposed to be stimulated to contraction.

Onset and duration of action.—Given by the mouth in small therapeutic doses the effects appear very slowly, and takes about 24 to 36 hours for the circulatory action, and 72 hours for the diuresis. But the appearance of digitalis effect depends largely upon the dose. Thus when full doses are given the effects appear within 2 to 4 hours. Digitoxin has the property of fixing itself to the heart muscle and once the fixation has taken place its removal is very difficult, in fact it cannot be removed by any chemical or physiological measure (Cloetta). Its products are eliminated from the cardiac muscle very slowly. It is for this reason that symptoms of poisoning may occur even though the dose may not be increased, provided the drug is continued for a prolonged period. Once established, the effects continue for some time even after the stoppage of the drug.

Cumulative action.—Digitalis is not given in sufficient doses for fear of cumulative action, for when given for a

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long time it sometimes shows symptoms of poisoning even when its dose has not been increased. This is known as the cumulative effect of the drug, and is due to the retardation of its excretion or destruction. The danger of cumulative action has been exaggerated, for the symptoms disappear in a few hours as soon as the use of the drug is discontinued. The active principles, not being eliminated as fast as they are absorbed accumulate in the system. The symptoms of excessive action are :—

1. Nausea and vomiting from stimulation of the vomiting centre.
2. A marked decrease in urinary secretion due to constriction of the renal vessels.
3. Headache.
4. A progressive slowing of the pulse rate from excessive vagus stimulation, which should never be allowed to go below 60.
5. The development of sinus arrhythmia, premature contractions, dropped beats (incipient heart-block) from depression of A. V. bundle, extra-systole, tachycardia and fibrillation from hyperexcitability of the cardiac muscle. In fact any form of cardiac irregularity may follow digitalis administration, and it becomes rather difficult to differentiate whether the irregularity is the result of digitalis administration or a part of the clinical picture.

When any of the above symptoms arise the administration of the drug should be at once stopped.

Elimination.—It is chiefly excreted by the kidneys and partly by the gastro-intestinal mucous membrane. But its elimination is very slow, often slower than its absorption, and its long continued use may cause cumulative effects.

Toxic action.—Large doses cause nausea, vomiting, and purging; the vomit is grass-green, the change in colour being probably due to the action of gastric juice on some ingredients of digitalis. The other symptoms have already been described.

Antidotes.—Emetics or pump. Strong coffee, or tannin in solution and in large draught. Stimulants—alcohol, ammonia, etc. Warmth to the extremities. To check excessive vagus action atropine $\frac{1}{60}$ gr. hypodermically. Opium. Absolute rest and recumbent position are essential.

THERAPEUTICS

Valvular diseases of the heart.—Digitalis is a valuable drug in diseases of the heart. It is of supreme value in those conditions of the heart which have departed most widely from the normal. If the muscles are healthy, but otherwise over-worked, exhausted and fatigued, digitalis by its effect on the cardiac muscle will restore its tone. In valvular diseases of the heart where the incomplete emptying has caused the ventricles to dilate and there is an over-increasing strain on the muscle, digitalis has a wonderful

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influence in restoring the dilated and weakened ventricle to a state of efficiency. Under its use a quick, weak and irregular contraction becomes slower, stronger and regular. As the diastolic period is prolonged, the heart gets more time for nutritive repair, and for more efficient subsequent contraction, from the flowing in of more blood from the dilated auricle. Since digitalis acts by its powerful effects on the cardiac muscle, it is of greater value in ventricular dilatation which follows **mitral and tricuspid regurgitation** than in auricular dilatation. Digitalis therefore relieves dyspnœa, cough, venous engorgement of the lungs and of the abdominal organs, œdema, dropsy, and many other symptoms due to mitral regurgitation. It also benefits mitral constriction, as by lengthening the period of diastole it allows the normal amount of blood to pass through the constricted orifice.

In the first stage of aortic regurgitation digitalis is considered useless or positively harmful as it prolongs the diastolic interval and thus allows more time for the blood to flow back from the aorta. In most cases, however, the period of diastole is not prolonged, and clinical evidence shows that in some cases of aortic valve failure digitalis is of undoubted value. In the second stage, when the ventricle dilates, and the auriculo-ventricular orifice enlarges, producing secondary mitral regurgitation, digitalis is of great value. But it must be given with great caution, for sudden syncope may occur if the patient does not keep to his bed. Cases of pure obstruction do not require any drug, as compensatory hypertrophy may gradually take place without them. But when we wish to increase the contractile force of the heart in order to drive more blood through the obstructed aorta, or when from such an obstruction mitral disease has set in, digitalis in small doses does immense good.

Another great field of usefulness of digitalis is in **cardiac irregularities.** It is of great value in **auricular fibrillation** which occurs in advanced myocardial and valvular lesions. In this condition the over-stretched auricular muscles are unable to make concerted contraction and the impulses arise in abnormal parts of the auricle, and the auricle is kept in continual inco-ordinate activity. These numberless irregular impulses pass into the ventricle and the ventricle responds without any regularity in rhythm or strength. Digitalis acts as a charm in this condition, rapidly quieting the mad irregularities of the heart. Fifteen to thirty minims, three or four times a day, should be given at first, and if the fibrillation is permanent, should be followed by smaller doses once or twice a week, or once a day for some time. It acts by impairing the conductivity of the auriculo-ventricular bundle, *i.e.*, by establishing partial heart-

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block, whereby many of the superfluous auricular impulses are blocked and do not pass to the ventricles.

Digitalis is also of great value in **auricular flutter.** In this condition the auricle is also the seat of abnormal excitation, and beats at a very rapid rate though regularly. Given in full doses, digitalis will change the flutter into fibrillation and by reducing the conductivity of the bundle of His makes the ventricles beat slowly.

Digitalis is contra-indicated in **partial heart-block** as it tends to increase the degree of block. But opinions differ in complete heart-block, indeed some authorities recommend it on the ground that by slowing the rate of the auricle and increasing that of the ventricle it will help to bring the auricular and ventricular rates more nearly together. It is to be avoided in *bundle-branch block* and in *sino-auricular block.*

Fatty heart.—Digitalis should not be given in **fatty degeneration** of the heart, as the increased force of systole may lead to rupture of the degenerated muscle fibres.

Other cardiac diseases.—In many primary diseases of the muscular structure, such as acute or chronic **myocarditis,** with or without vegetative growths, **pericarditis, endocarditis** with or without valvular lesions, digitalis helps to quiet and regulate the action of the heart. Many **functional diseases** of the heart, such as palpitation, irregular cardiac beat due to dyspepsia, are benefited by digitalis, but it must be used with caution as it may bring on indigestion. In many **irritable conditions** of the heart, especially in persons who take excessively hard exercise, such as rowing or long marches with heavy knapsacks, or in persons of a neurotic temperament, digitalis is considered highly beneficial. The dilatation of the right side of the heart which so often accompanies chronic diseases of the lungs is also relieved by digitalis.

Digitalis as a diuretic.—Digitalis is the most reliable and often successful diuretic in **cardiac œdema,** and the majority of cases require no further medication. Remarkable results follow rapid digitalization, although the changes in the rate of the heart and occurrence of diuresis may not necessarily run together. Since digitalis causes constriction of vessels, including those of the kidneys, in large doses, massive doses do not necessarily act more efficiently though the effects are often more dramatic. It also acts as a diuretic in **nutritional** and **anæmic œdemas** where the circulation is impaired. It is however of not much use as a diuretic in dropsies from other causes, *e.g.* in Bright's disease, where the drugs of the purin group are generally preferred. But in chronic Bright's disease when the anuria is the result of deficient circulation, digitalis, especially the Guy's pill is of great service. Since therapeutic doses do not materially

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alter the blood-pressure, high arterial pressure *per se* is no contra-indication to the use of digitalis.

Nervous diseases.—In sleeplessness at night followed by drowsiness in the day, in anæmic patients, digitalis may act as a hypnotic by restoring tone to the relaxed vessels.

Acute febrile diseases.—Digitalis is often used in different febrile diseases where the heart becomes affected from the toxins of the infection or from high temperature. In these conditions digitalis may be used to improve the tone of the heart and produce slowing of its rate. Its use has also been advocated in pneumonia, but the different factors such as high temperature, toxins, or the invasion of the heart with specific organisms exert an influence over the heart which digitalis cannot overcome. It has therefore been suggested that it should be used from the very commencement on the idea that if digitalization of the heart is done early it will prevent the toxin from affecting the heart. It is however debatable whether early digitalization will reduce the case mortality in pneumonia.

Exophthalmic goitre.—Whether given alone or with iron and quinine, digitalis is considered to be a valuable remedy in this disease, but very often it is found to produce little effect.

Caution.—It should be remembered while treating cardiac disturbances, that the effect of digitalis varies in different classes of cases, that while it is of great value in certain diseases of the heart, its effects are not so marked in others, and in a third class of cases its use is contra-indicated—being harmful or dangerous. Great care and caution should therefore be observed in the selection of cases for the exhibition of digitalis. The best way to avoid any untoward effect during a course of digitalis treatment is to suspend the administration of the drug for a few days as soon as the physiological reaction is reached, as evidenced by nausea, vomiting, diarrhœa and slow pulse. In this way the cumulative action is avoided. Cases of sudden deaths are on record when the drug has been pushed without stoppage after it had affected the heart.

It is contra-indicated in partial heart-block, cerebral hæmorrhage, embolism of recent origin and aortic aneurism in its later stages; and should be used with caution in pronounced arterio-sclerosis.

Prescribing hints.—Digitalis is best prescribed in the form of tincture, which should be given alone in 15-30 ms. doses three times a day to be diluted with water before taking, because the tincture does not maintain its strength long when kept diluted in water. This dose should be pushed till a definite response is observed in either the pulse, the urine, or the nausea, when its use should be stopped and the heart-rate carefully watched. When the heart-rate shows

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signs of increase, half the dose should be given and the dose regulated as occasion arises aiming to maintain compensation and keeping the pulse to about 80, with the smallest possible dose. It should be noted that practically no therapeutic effect is produced until the total dosage nearly approaches the toxic. As a rule no beneficial effects are observed till the second or third day. It has therefore been suggested that in urgent cases, who have not received any digitalis previously for 10 days, a single large dose followed by smaller doses until some definite response is obtained, should be preferred. The other method of giving digitalis is that of Eggleston. He gives 7.5 c.c. of the standardised tincture per 100 pounds of body weight as the first dose ; followed in six hours by one-fourth of the total dose, then smaller fractions every four or six hours till full response is reached. With this method the effects appear within 2 to 5 hours after the first dose, reaching its maximum within 24 hours. This effect may continue for 14 to 15 days without further administration. The amount of digitalis required to produce the maximum effect in man is determined by the following formula of Eggleston.

$$\frac{CU \times 0.15 \times W}{100} = \text{c.c. of tincture in total amount}$$

CU = no. of milligrams of digitalis used in 1 cat unit
W = weight of patient in pounds

If the cat unit value is unknown, it may be taken to be 100 for a good tincture.

Although digitoxin and digitalin are insoluble in water, the infusion contains some of them in colloidal solution brought about by digitonin, which, though not absorbed from the intestine, helps the solution of other glycosides. Since these glycosides undergo decomposition and form resin-like bodies when kept in solution for long, old preparations, specially the infusion, are useless therapeutically and may be harmful.

Diuresis generally follows the administration of digitalis in cases of heart failure, and if there is no diuresis, the use of the drug will not produce any beneficial results. In fact the secretion of urine is not increased unless there is œdema present, although digitalis may be given even in massive doses.

Since therapeutic doses do not raise the blood-pressure, high blood-pressure is not a contra-indication to the use of digitalis, although the pulse pressure may be increased as a result of the fall in the diastolic level in cases of heart failure.

Though incompatible with iron on account of the tannin it contains, digitalis is often advantageously given with iron ; but the resulting inky mixture should be cleared by the addition of diluted phosphoric acid.

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STROPHANTHUS

Strophanthus

Syn.—Strophanthus seeds.

Source.—The dried ripe seeds of *Strophanthus kombe* freed from the awns.

Characters.—Lanceolate to linear-lanceolate, acuminate, about 12 to 18 mm. long, 4 mm. broad, blunt base, tapering apex, sides flattened, one side having a median ridge and the other being convex, covered with silky appressed hairs. Characteristic odour. Taste, very bitter.

Composition.—It contains from 7 to 10 p.c. of a mixture of glycosides, *K-Strophanthin*, together with about 25 p.c. of fixed oil. K-strophanthin consists of cymarin, k-strophanthin-β and other glycosides, and yields on hydrolysis with dilute mineral acid strophanthidin and a biose. *Choline*, oil and resin.

Official Preparation

1. **Tinctura Strophanthi.**—It is equivalent in activity to a 0.42 p.c. solution of the International standard ouabain. **B.P. Dose.—2 to 5 ms. or 0.12 to 0.3 mil.**

STROPHANTHINUM

Strophanthin

Syn.—Kombe Strophanthin.

Source.—A mixture of glucosides obtained from Strophanthus.

Characters.—A white, or yellowish white powder, minute crystals being visible under microscope. Moderately *soluble* in water, and in alcohol (90 p.c.), less so in dehydrated alcohol. Solution in water or alcohol is neutral to litmus, and is dextrorotatory.

B.P. Dose.—$\frac{1}{240}$ to $\frac{1}{60}$ gr. or 0.00025 to 0.001 grm. by intramuscular or intravenous injection.

Pharmacology

Locally.—Strophanthin is an irritant to the mucous membrane, but less powerful than digitalis glycosides. On the other hand it has an anæsthetic action on the conjunctiva and cornea, and was used as such before the introduction of cocaine.

Internally.—Although strophanthus is absorbed more rapidly than digitalis and does not produce any local irritation to the same extent as digitalis, it is easily destroyed by the digestive juices, and loses much of its effects when given by the mouth.

Heart and circulation.—Action exactly *similar to that of digitalis.* Its action is very rapid, producing its effect within half to one hour. But it is more dangerous since it induces more readily the condition known as "delirium cordis," and its absorption and elimination are very uncertain. It has no effect on the peripheral vessels and therefore does not cause vaso-constriction like digitalis.

Kidneys.—It is a diuretic in a normal person, and as it raises the blood-pressure without constricting the peripheral

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renal vessels it sends more blood through the kidney and acts as a more efficient diuretic than digitalis. Like other glycosides it is partly destroyed in the body and is readily excreted from the heart and muscle and therefore its action is short and is not cumulative.

Therapeutics

Strophanthus was introduced by Fraser as a substitute for digitalis, but it has not come up to the expectations formed of it.

In the treatment of mitral disease *the rule is to begin with digitalis* and then change to strophanthus if the former disagrees. In the treatment of failing compensation, it will be found a highly satisfactory plan to give strophanthin intravenously. The tincture becomes inert in a few days when mixed with water, and should therefore be prescribed by itself to be taken diluted with water. But on account of the uncertainty of its absorption its use is becoming rare nowadays.

Strophanthin being soluble in water and more uniform in composition is largely used intravenously combined with glucose solution. By its use the amplitude of the pulse-wave is increased, the pulse becomes fuller and regular, and the symptoms of cardiac failure disappear. It is specially indicated in the failure of the heart in an advanced cardiac disease. This method is however not suitable where a prolonged treatment is necessary, when digitalis will be found more convenient. With digitalis the effect of gradual absorption is more beneficial to the heart than the daily use of the intravenous injection.

SCILLA

Squill. *N.O. Liliaceæ*

Source.—The bulb of *Urginea Scilla*, divested of its dry membranous outer scales, cut into slices, and dried.

Characters.—In curved, very pale yellow, somewhat translucent strips, tapering towards both ends, from 0·5 to 5 cm. long; pulverisable when dry, not when moist. Inodorous, bitter.

Composition.—(1) *Scillitin*, which is purified form of *Scillitoxin*; and (2) *Scillidiuretin*, both amorphous glycosides. (3) *Scillin*, an inactive glycoside.

B.P. Dose.—1 to 3 grs. or 0.06 to 0.2 grm.

Official Preparations

1. **Acetum Scillæ.—10 p.c. B.P. Dose.—10 to 30 ms. or 0.6 to 2 mils.**
2. **Oxymel Scillæ.—Active constituents equivalent to 5 p.c. w/v of squill. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**
3. **Syrupus Scillæ.—Equivalent to 4.5 p.c. w/v of squill. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**
4. **Tinctura Scillæ.—Equivalent to 10 p.c. w/v of squill. B.P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

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Pharmacology

Internally.—Squill acts like digitalis in many respects. The description of the latter will therefore apply to that of the former with the following distinguishing characteristics :—

1. Its action on the heart is almost the same as digitalis and when given intravenously causes a greater rise of blood-pressure; but administered by the mouth its absorption is slow and less complete and therefore its effect on the heart is not so marked.

2. It is a *more powerful gastro-intestinal irritant than digitalis*, causing nausea, vomiting, purging (even bloody stools), and intense inflammation of the mucous membrane in full doses, and occasionally in medicinal doses. In many cases this irritant effect is not observed.

3. It is an *expectorant* acting reflexly through gastric irritation.

4 It is a *more powerful diuretic* than digitalis. It acts in two ways :—*(a)* like digitalis by improving the circulation, and *(b)* the active ingredients being excreted by the kidneys act as direct stimulants to the renal cells, and may cause considerable irritation of these organs.

Therapeutics

Internally.—Squill can be given in cardiac and other forms of **dropsy**. But its irritant properties are somewhat mitigated when it is combined with digitalis. Even then it is safe to occasionally suspend its administration for a while. Guy's pill is an excellent combination, and an efficient diuretic in **cardiac dropsy.**

It is rarely prescribed alone and is contra-indicated in acute renal disease or if there be gastro-intestinal irritation.

It is largely used as expectorant, but should not be given in acute bronchitis. It is of great value in **old-standing pulmonary diseases**, where, besides acting as an expectorant, it tones up the heart the right side of which is so frequently dilated. In the **chronic bronchial affections** of children, the oxymel or syrup is always serviceable in 10 to 15 m. doses, but its indiscriminate use in all varieties of bronchial affections is to be deprecated. Squill becomes doubly beneficial in chronic catarrh of dropsical patients.

APOCYNUM

(Not official)

Syn.—Canadian Hemp.

Source.—Root of *Apocynum cannabinum.*

Composition.—It contains the glycosides *cymarin*, to which its action is due, and *apocynin.*

Dose.—1 to 5 grs. or 0·06 to 0.3 grm. of powdered root.

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Non-official Preparation

1. **Tinctura Apocyni, B.P.C.**—1 in 10. *Dose.*—5 to 10 ms. or 0.3 to 0.6 mil.

Pharmacology and Therapeutics

Apocynum is a gastro-intestinal irritant in large doses, giving rise to nausea, vomiting and purging.

It possesses all the properties of digitalis on the circulation but the effects on the vaso-constrictor are relatively strong. It directly stimulates the unstriped muscles. It is a powerful **diuretic** and is largely used in **cardiac dropsies.** It is also recommended in dropsies due to cirrhosis of the liver and is also useful in causing the absorption of **pleuritic effusion.** For these reasons it is commonly known in America as the "Vegetable Trocar."

2. Cardiac Depressants

Excepting the central nervous system the heart is more liable to be affected by poisonous drugs than any other tissues of the body. When the heart is depressed, the force of contraction becomes less strong, the conduction is diminished, and the rate is reduced. The reduction of the rate of the heart without depressing the force of the contraction is often desirable in disease. Quite a large number of drugs act as cardiac depressants. All hypnotics and general anæsthetics also act as cardiac depressants, and those containing chlorine molecule are more so.

ACONITUM

Aconite

Syn.—Monk's Hood. **Syn. I.V.**—*Katbis, Dudhiabish*, Hind.

Source.—Dried root of *Aconitum Napellus.*

Characters.—Dark brown, obconical; usually 4 to 10 cm. long, from 1 to 3 cm. wide at the crown, to which is attached the base of stem or a bud and showing root scars. Internally, starchy, showing a stellate cambium. Odour, slight; taste, slight, followed by a persistent tingling and by numbness.

Composition.—(1) *Aconitine* (acetylbenzoyl-aconine), the chief active principle. (2) *Picraconitine* (Benzoyl-aconine). (3) *Aconine.* (4) *Aconitic acid* and starch.

Official Preparation

1. **Linimentum Aconiti.**—0.2 grm. of the alkaloids in 100 mils.

Non-official Preparations

1. **Chloroformum Aconiti, B.P.C.**—Root 100, Dilute Ammonia Solution 25, Absolute Alcohol and Chloroform, each *q.s.* to 100. Mixes with oils and liniments. A powerful sedative in neuralgia, etc.

2. **Tinctura Aconiti.**—1 in 10. Contains 0.04 p.c. ether-soluble alkaloids. *Dose.*—2 to 5 ms. or 0.12 to 0.3 mil.

3. **Linimentum Aconiti Comp.** *Syn.—A.B.C. Liniment.*—Aconite, Belladonna and Chloroform liniment, equal parts.

Pharmacology

Externally.—When applied to the skin rubbed up with chloroform or some fatty substance, without which it is not absorbed, aconite first stimulates then paralyses the termina-

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tions of the sensory nerves, thereby causing tingling, numbness and anæsthesia. It is rapidly absorbed from all mucous surfaces.

Internally. **Gastro-intestinal tract.**—The same tingling, numbness and anæsthesia are produced when aconite is applied to the tongue, followed by salivation caused reflexly through irritation of the nerve-endings of the tongue and nausea. In large doses it causes gastro-intestinal irritation such as nausea, vomiting and diarrhœa.

Heart and circulation.—In small doses it makes the heart slow, diastole is prolonged and the systole is weakened. The pulse becomes weak and soft and if the dose is not increased does not become irregular. The slowing is due to stimulation of the vagal centre and does not occur if the vagus is cut. According to Cushny aconite has no influence in slowing the rate of the heart in ordinary doses, in fact there is some quickening when maximum therapeutic doses are used through the nausea induced by the irritant effect in the stomach. In large doses it has a direct effect on the heart muscle, and the heart becomes feeble, irregular and accelerated, auricular-ventricular arrhythmia being set up, and it finally stops in diastole. These effects of aconite cannot be elicited in man in therapeutic doses and are due to the direct action on the cardiac muscle. The **blood-pressure falls** chiefly from lessened output from cardiac depression in the early stage, while later the vaso-motor centre is also paralysed.

Respiration.—In small doses it stimulates the respiratory centre, and breathing becomes deep and frequent, but it is soon followed by depression when the respiration becomes slow, deep, irregular and laboured. Death takes place from **asphyxia** due to respiratory failure from paralysis of the centre.

Temperature.—A febrile temperature is lowered by aconite; the mechanism of this effect is not well understood, but increased diaphoresis is one of the factors.

Nervous system.—Whether applied locally or taken internally, aconite first stimulates and then depresses the periphery of the sensory nerves. The ends of the motor nerves are also somewhat stimulated and then depressed, and the nerves conveying thermic sensations are affected in poisoning. It first stimulates but soon depresses, the vagal, vaso-constrictor and respiratory centres. The brain remains unaffected. The pupils first contract, then dilate. Large doses first stimulate and then depress the motor centres in the spinal cord. The convulsions observed in poisoning are due to asphyxia.

Skin.—Perspiration is increased possibly due to dilatation of the vessels of the skin. It sometimes gives rise to an erythematous rash.

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Elimination.—It is mostly excreted in the urine, although traces of the active principle have also been detected in saliva, stomach, bile and sweat.

Acute toxic action.—Within a few minutes after swallowing a poisonous dose of aconite, severe tingling and burning followed by numbness are noticed in the mouth and gullet. Intense abdominal burning; vomiting; cold, clammy skin and profuse sweating; tingling, formication, and numbness of the skin; small, feeble, irregular pulse; fixed, staring eyes with dilated pupils; difficult respiration; muscular weakness; prostration; fainting; sometimes convulsions; lastly death either from asphyxia or occasionally from syncope—are the symptoms of poisoning by the drug. Consciousness remains, more or less clear, till death.

Antidotes.—Emetics, pump, stimulants, hot bottles, friction, sinapisms to the heart. Tr. digitalis 20 to 30 ms., strychnine up to $\frac{1}{30}$ gr. and atropine may be used. Amyl nitrite inhalation is recommended by Murrell.

Physiological antagonists.—Digitalis, strychnine, atropine, ammonia, ether and alcohol.

Benzaconine.—It is bitter and less toxic and does not cause tingling. It slows the heart-beat the ventricles contracting once for every two or three auricular contractions. It interferes with the motor nerves and does not paralyse the sensory nerves.

Aconine, though bitter, does not cause numbness or salivation. It strengthens the ventricular systole and opposes inco-ordination of the heart-beat caused by aconitine. In large doses it depresses respiration and paralyses motor nerve-endings like curara.

THERAPEUTICS

Externally.—Aconite in the form of a liniment is applied for the relief of pain in neuralgia, sciatica, muscular rheumatism and inflammatory joint affections. The addition of chloroform increases the efficacy, as it facilitates absorption. For this reason, Chloroformum Aconiti, B.P.C. or the A.B.C. liniment are more effective than the B.P. preparation.

Internally.—Aconite is not so largely used now in fevers as formerly. Careful observations by Mackenzie and Price failed to elicit any slowing of the rate of the heart with aconite and it is rarely used in the treatment of fevers. Nowadays its use is confined chiefly to **inflammatory fevers,** such as pleurisy, peritonitis, tonsillitis, sore throat, etc. It should be given in small doses (1 or 2 ms. of the tincture) rather frequently until there is a fall of temperature, sweating and relief of the symptoms. It should never be given in continued fevers, such as typhoid.

CLASS B: Drugs acting on the Vessels

The arteries are elastic nervo-muscular tubes, whose calibre constantly changes owing to a variety of influences, which are transmitted by the vaso-constrictor and vaso-dilator nerves, from the vaso-motor centre located in the medulla, and certain subsidiary vaso-motor centres in the spinal cord. The arterial muscles are kept in a constant

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state of contraction or tone, which enables them to counteract the pressure of the fluid within. This tone is chiefly due to continuous reception of subminimal impulses from the vaso-constrictor centre. The vaso-dilators differ from the constrictors in that they are not in tonic activity, and that they produce dilatation by inhibiting the contractile impulses, the arteries having no dilator muscles. Both the constrictors and dilators belong to the autonomic system, and when both sets are stimulated the constrictor effect predominates, but if the stimulation is prolonged, the constrictors are the first to show signs of exhaustion, so that eventually there is dilatation.

The vaso-motor system may be influenced by drugs acting upon any part from the centre to the nerve-endings, and also reflexly by afferent impulses coming to the centre from other parts of the body. It should be noted however that some of the arteries—the coronary, pulmonary and cerebral—have no vaso-constrictor nerves. But the maintenance of efficient coronary circulation is most essential, as on this depends the activity of the heart.

By the *blood-pressure* is meant the pressure to which the walls of the arteries are subjected. The rise and fall of the blood-pressure depend upon the activity of the vaso-constrictor and vaso-dilator nerves respectively. Besides the afferent influences affecting the pressure there are other circumstances which greatly modify it. They are (1) the heart's output in a given time; (2) the total quantity of blood in the circulation; (3) the peripheral resistance; and (4) the viscosity of the blood.

The pressure may be raised by (1) general constriction of the arterioles; (2) increase in heart's output; (3) increased volume of blood; and (4) slightly by increased viscosity of the blood. The pressure is lowered by the opposite conditions.

The arterioles, specially those of the splanchnic area, are the most important regulators of the arterial pressure so that when these arterioles dilate so much blood passes into them that no blood is left for the brain and other vital organs, thus causing faintness and even death. Even when the arterioles remain contracted the pressure cannot be maintained if the heart fails, or if there is much loss of blood.

Capillaries.—Since the normal exchanges between the blood and the tissues take place through the capillary walls, maintenance of efficient capillary flow is an important function of the circulatory organs. The arterioles being actively contractile act as flood-gates and regulate the amount of blood passing through any given set of capillaries. The capillaries themselves are capable of contraction and dilatation and are controlled by chemical and nervous stimuli, and though controlled by sympathetic are not affected by adrenaline beyond a certain distance from the arterioles. Pituitary

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extract is supposed to contain a hormone which maintains the normal tone of the capillaries. Histamine, arsenic and antimony dilate the capillaries. Of these arsenic in poisonous doses dilates the capillaries of the splanchnic area and causes a fall of blood-pressure. Dilatation of the capillaries of the splanchnic area is also the cause of fall of blood-pressure in surgical shock.

Carotid Sinus.—This is the name given to a dilatation normally present at the bifurcation of the common carotid artery. Recent studies by different observers have elucidated its importance in the regulation of circulation and respiration. It has been pointed out by Heymans that the regulation of blood-pressure through adrenaline secretion is controlled reflexly by the sinus nerves which normally exert a tonic inhibitory influence on the vaso-motor centre. He has further shown that neither the adrenal glands nor the centres controlling them are acted on directly by the level of the blood-pressure. A rise of pressure in the sinus inhibits and a fall of pressure in the sinus stimulates adrenaline secretion. During rest the sinus nerves exert a tonic inhibitory influence over adrenal activity.

Drugs which raise the blood-pressure

1. *Acting by stimulating the vaso-motor centre.*—All drugs which stimulate the central nervous system also stimulate the vaso-motor centre in the medulla. They cause a rise of blood-pressure by constricting the vessels of the splanchnic area. It is possible that these drugs increase the output of adrenaline. The drugs belonging to this group are strychnine, caffeine, digitalis, camphor, etc. Alcohol given in concentrated solution stimulates the vaso-motor centre reflexly and causes a rise of blood-pressure. After absorption the peripheral vessels dilate and there is a fall of pressure. Excess of CO_2 in the blood, as happens in asphyxia, also stimulates the centre. The centre may be reflexly stimulated by counter-irritants.

2. *Acting on the vaso-motor nerve-endings.*—The normal tone of the vessels depends upon the activity of the adrenal glands, and removal or disease of these glands is followed by fall of pressure. Adrenaline, ephedrine and ergotoxine cause powerful vaso-constriction and a rise of pressure by acting on the sympathetic nerve-endings. Ergotoxine however causes subsequent depression and paralysis of the augmentor nerve-endings of the sympathetic and causes a fall of pressure.

3. *Acting on the muscles.*—These when administered either by the mouth, or as injection, cause vaso-constriction by acting on the muscles of the vessels. They are digitalis, pituitary extract, barium and veratrine.

4. *By increasing the volume of blood.*—During collapse and shock specially from hæmorrhage the pressure diminishes

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which can be raised by (*a*) *transfusion of blood*; and (*b*) *injection of normal saline.* But since saline infusion has a tendency to diffuse into the tissues, the excess of fluid is readily excreted by the kidneys. A more permanent increase of blood volume is obtained by adding some colloid in the transfused fluid, as injection of gum saline (*see* page 83).

Drugs or measures which lower the blood-pressure

1. *Acting by depressing the vaso-motor centre.*—Alcohol, chloral hydrate, ether, chloroform and narcotics depress the vaso-motor centre and cause a fall of pressure. They cause the vessels of the skin to dilate with consequent loss of heat. Coal tar antipyretics also produce the same effect. Surgical shock which occurs immediately after an injury is followed by a fall of blood-pressure which has been attributed to exhaustion of the vaso-motor centre which does not respond to normal afferent stimulation.

2. *Acting on the arterial muscle.*—These drugs when used subcutaneously, or taken by the mouth, or some of them when inhaled, dilate arterioles and cause a fall of pressure. Certain products of metabolism also cause vaso-dilatation, as happens with slight increase of acidity of blood. Drugs belonging to this group are amyl nitrite and nitrites, organic nitrates, choline, theobromine, and arsenic in poisonous doses

3. *Acting by diminishing the volume of blood.*—This may be done by bleeding, venesection or by application of leeches. The volume of circulating blood may be reduced by diminishing the plasma. Purgatives and diaphoretics by withdrawal of fluids from the body reduce plasma volume.

4. *Acting by causing capillary paralysis.*—Histamine has a special toxic effect on the capillaries which are dilated causing a fall of pressure although the arterioles are constricted. By producing abnormal permeability of the capillaries it helps plasma to pass from blood to the tissues. Secondary shock also causes a fall of blood-pressure and is supposed to be due to the production by the tissues of some substance having action similar to histamine.

Drugs or measures acting locally on the vessels

1. *Local vascular stimulants*, or remedies which dilate arterioles when locally applied to them. They are alcohol, iodine, ammonia, tartar emetic, arsenious acid, camphor, cantharidin, capsicum, phenol, creosote, croton oil, chloroform, ether, mustard, volatile oils, hot applications, etc.

2. *Local astringents, hæmostatics or styptics* are drugs which constrict the vessels when locally applied. They also cause shrinkage of the mucous surface. Those acting by contracting the muscular fibres are adrenaline, cold from any means as evaporation of ether, ethyl chloride, or by application of ice. Vegetable astringents, alum, silver, lead, iron, etc., act by coagulating the proteins in the tissues

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surrounding the vessels. They have no action on the muscular coat of the vessel walls.

1. Drugs Raising the Blood-pressure

Vaso-constrictors

ADRENALINA

Adrenaline

Syn.—Epinephrine ; Suprarenin : Adnephrine.

Source.—It is *l-α-3* : 4-dihydroxyphenyl-β-methylamino-ethanol. An active principle of the suprarenal gland. Obtained from an acid extract of the glands of certain mammals, or by synthesis.

Characters.—A colourless or pale buff-coloured, sphæro-crystalline powder. Sparingly *soluble* in water ; *insoluble* in alcohol (90 p.c.) and in ether. *Soluble* in aqueous solutions of mineral acids, and of sodium and potassium hydroxides. Not stable in neutral alkaline solutions, which becomes red on exposure to air. Natural adrenaline is lævo-rotatory.

B.P. Dose.—$\frac{1}{600}$ to $\frac{1}{120}$ **gr. or 0.0001 to 0.0005 grm.**

Official Preparation

1. **Liquor Adrenalinæ Hydrochloridi.** *Syn.—Liq. Epinephrinæ Hydrochloridi. U.S.P.*—1 in 1000. To be kept in amber-coloured glass bottles. **B.P. Dose.—2 to 8 ms. or 0.12 to 0.5 mil subcutaneously.**

Non-official Preparations

1. **Unguentum Adrenalinæ et Cocainæ, B.P.C.**—Adrenaline, 0.1 gm. ; boric acid, 0.2 gm. ; cocaine hydrochlor. 1.0 gm. ; distilled water, 3 mil. ; lanoline 50 gm. ; white soft paraffin, 45.7 gm.

2. **Nebula Adrenalini Aromatica, B.P.C.** *Syn.—Adrenaline Inhalant.*—Adrenaline 8¾ grs., absolute alcohol 2½ oz., eucalyptol 1 oz., oil of gaultheria 192 ms., hydrochloric acid *q.s.* to dissolve adrenaline, castor oil 10 oz., arachis oil to 20 oz. A soothing and astringent application to the nasal mucous membrane. To be used with an atomiser.

3. **Nebula Adrenalini et Cocainæ, B.P.C.**—Adrenaline chloride solution 4 oz., cocaine hydrochloride 87½ grs., chlorbutol, 35 grs., sodium chloride 63 grs., water to 20 oz. A sedative and hæmostatic.

4. **Suppositorium Adrenalini.**—Contains adrenaline 1/60 gr. in. each. Those with cocaine contain ¼ gr. of cocaine in addition to above.

Pharmacology of Adrenaline

The main action of adrenaline is stimulation of the sympathetic nerve-endings, both motor and inhibitory. It therefore produces effects on all the organs of the body.

Applied locally to mucous surface adrenaline causes blanching by powerfully **constricting the capillaries** of the part due to stimulation of the vaso-constrictor nerve-endings of the arterioles at the site of application. Given by the mouth it has no systemic effect, possibly by constricting the arteries it prevents its own absorption. The slow absorption helps the destruction of the drug in the stomach before it reaches the circulation. Although it is rapidly destroyed some hold that if retained in the mouth it is sufficiently

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absorbed by the sublingual tissues to produce its systemic effects, chiefly rise of blood-pressure and dilatation of the bronchial muscles. This however is doubtful.

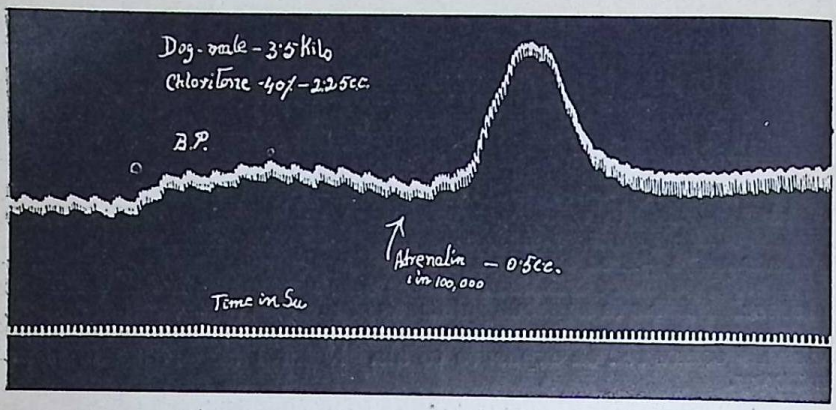

Fig.—3. Showing effect of Adrenaline on Blood-pressure in dog. ½ c. c. of 1 in 1,00,000 solution was introduced into a vein. Note the sudden and precipitate rise of pressure and equally sudden fall. Cf. effect of Ephedrine, page 283.

Heart and circulation.—Injected intravenously it causes a **rise of arterial blood-pressure.** The pressure rises sharply and as it reaches the maximum the heart beats are strengthened and slowed. If the vagi are intact, as in normal animal, the rise is much less marked and is accompanied by definite slowing of the heart. The pressure however is not sustained and returns to normal quickly. If a second injection is given when the pressure is already high it sometimes causes a fall instead of the usual rise. If the sympathetic myoneural junction is paralysed by the previous use of ergotoxine an injection of adrenaline causes a distinct fall of pressure (*see* Ergotoxine). The rise of pressure is due to **constriction of arterioles** from the direct action of the drug on the myoneural junctions in the muscular coat of the vessel walls. The constriction is most marked in the smaller vessels, although the larger vessels and even the veins participate. The intensity of action depends upon the relative preponderance of the sympathetic innervation, and in the intact animal the main constrictor effect falls on the richly supplied splanchnic area, the skin and the kidneys, and the minimum on the pulmonary and cerebral vessels. The coronary vessels are usually dilated, but very small concentrations cause contraction and diminish the flow of blood to the heart.

The **heart** is accelerated at first, then becomes slow, and finally becomes accelerated again. The quickening is the result of stimulation of the sympathetic endings in the heart muscle and is accompanied by more powerful contraction and

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complete emptying of the cavities. The slowing is due to excitation of the cardio-inhibitory centre in the medulla, as it is lessened on cutting the vagi and entirely disappears under atropine, and is due to stimulation of the centre by increased blood-pressure. As the coronary vessels are not constricted, rather dilated, the heart muscle gets more nutrition and the tone is improved, while its oxygen metabolism is also increased in proportion to its activity and rate. It has however the drawback of favouring the occurrence of fibrillation, specially when used before chloroform anæsthesia. In fact toxic doses produce auricular and ventricular fibrillation.

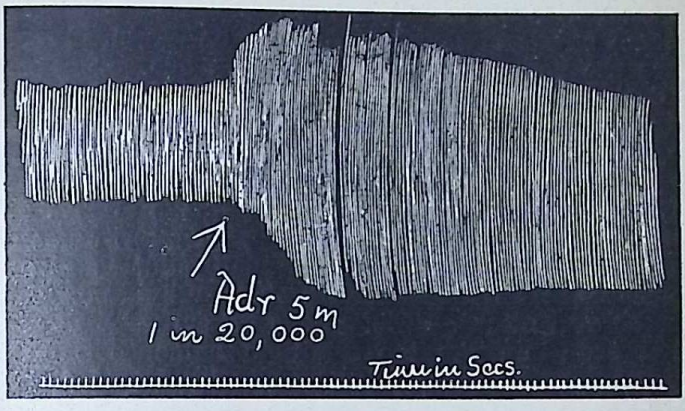

Fig.—4. Record of the movements of an isolated Rabbit's Heart during perfusion, showing effect of Adrenaline. Note the great acceleration and increased force of beat.

Eye.—Solution of adrenaline dropped into the eye causes the conjunctiva to become pale and shrunken, the eyelids retracted, and makes the eyeball appear more prominent. Given intravenously it causes dilatation of the pupil by stimulation of the sympathetic nerve-endings.

Respiration.—During the height of blood-pressure following an injection, the movements often cease and become shallow. This *adrenaline apnœa* is a reflex effect caused by the rise of blood-pressure which stimulates the afferent nerve-endings in the aorta and in the sinus caroticus and is not produced after cutting of the vagi or denervation of the sinus caroticus. In small quantities used hypodermically it causes increased depth of respiration. Applied locally to the excised rings of the bronchi of the ox it causes relaxation of the bronchial muscles by stimulation of the broncho-dilator (sympathetic) nerve-endings. In man a hypodermic injection causes a decided relaxation of the contracted bronchi.

Alimentary canal and liver.—Secretion of saliva is

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increased and corresponds in character with that due to stimulation of the cervical sympathetic. Glycogenic function of the liver is disturbed causing unusual hydrolysis of glycogen with an excess of sugar in the blood and tissues, and if this exceeds the renal threshold will give rise to glycosuria. After an intravenous injection adrenaline stimulates the ends of the splanchnics (sympathetic nerves to the alimentary canal) and lessens peristalsis of the stomach and intestine, but increases the contractions of the pyloric, ileocæcal and internal anal sphincters which receive the augmentor fibres from the sympathetic.

Uterus.—Adrenaline causes contraction of the uterine vessels and of the uterus itself when pregnant. The effect however varies with the different species of animals and in the same species, whether pregnant or virgin. It usually relaxes the non-pregnant uterus of cat, but causes contraction during pregnancy. Surviving human uterus is stimulated whether pregnant or not (Lieb, 1915). It relaxes the force of contractions of the human pregnant uterus specially during labour. Clinically, a hypodermic injection of 0.5 c.c. rarely causes any contraction, and abortion rarely follows when used for the relief of asthma in pregnant women.

Metabolism.—1.5 c.c. of 1 in 1000 solution given subcutaneously **raises the basal metabolism** by 20 p.c. in man.

Urine and sweat.—The vessels of the kidneys are contracted even in doses too small to influence the general blood-pressure. The secretion of urine is at first diminished but with the rise of pressure and subsequent relaxation of the renal vessels there is profuse **diuresis**, which continues for a little while even after the fall of the pressure. Urine often contains sugar due to an excess of sugar in the blood from lack of dextrose destruction, *i.e.* it is antagonistic to insulin. Sweat glands though supplied by the sympathetic are not affected by it.

Toxic action.—(*a*) *Major symptoms*:—Acute dilatation of the heart, pulmonary œdema, ventricular fibrillation and death. These usually follow intravenous injection if the heart is already weak and diseased.

(*b*) *Minor symptoms*:—These follow hypodermic use in susceptible persons. Palpitation, tachycardia, dyspnœa, rapid pulse, rise of blood-pressure, muscular tremors, nausea, vomiting, vertigo and cold sweats.

Therapeutics of Adrenaline

The chief use of adrenaline is as a local **hæmostatic**, and intravenously as a **circulatory stimulant** in collapse and shock. Its action being of very short duration, it is suitable only in *emergency practice*, and is not employed in ordinary conditions of failure of compensation. It may be added to saline infusion where there is considerable loss of blood, as in the treatment of cholera. In sudden stoppage of the heart in healthy persons, as for instance, in drowning and

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carbon monoxide poisoning, adrenaline injected directly into the heart may induce the heart to recommence beating, specially when accompanied with cardiac massage and artificial respiration. The intra-cardial injection should be given directly into the right ventricle, with a long fine needle, through the 4th intercostal space close to the sternum. Beneficial results have been recorded in cases of complete **heart-block** in five to ten minim doses given subcutaneously. It lessens the Adams-Stokes attacks and is worth a trial. Since chloroform increases the output of adrenaline, it should not be used in cardiac failure associated with chloroform anæsthesia as it may precipitate fibrillation of the heart.

It has been employed with success as a **local hæmostatic** to all kinds of bleeding surfaces, as in epistaxis, bleeding gums, piles, metrorrhagia, etc., and on account of its property of constricting the arterioles it is often combined with cocaine or eucaine in eye lotions and nasal sprays. The prolonged use of adrenaline moreover as an eye lotion is apt to set up troublesome chemosis of the conjunctiva and lachrymation. As an internal hæmostatic it is useless.

It is often combined with cocaine and other local anæsthetics to prolong the effect of the latter, and at the same time to reduce the chance of bleeding and toxicity by retarding absorption. The usual concentration necessary is ½ to 1 minim of the liquor in 20 minims of the solution *(see* cocaine, page 249*)*. Some patients suffer from palpitation, tremors, rapid pulse, etc., which however soon pass off and are due to idiosyncrasy. Moreover it has the drawback of producing local gangrene.

There is no satisfactory evidence that adrenaline is absorbed by the alimentary tract. This limits its use for oral administration to œsophageal spasm, gastrostaxis and vomiting, when it acts locally on the appropriate sympathetic endings. It is also given to stop hiccough. Its use has been suggested in exophthalmic goitre, but the results obtained so far have not been very satisfactory.

As it relaxes the bronchioles it is especially valuable in **spasmodic asthma** when given hypodermically in ½ to 1 c.c. doses of 1 in 1000 solution. It is also used in urticaria, angioneurotic œdema, anaphylactic shock, hypoglycæmia following the use of insulin, and to prevent the occurrence of **nitritoid reaction** which may appear after the use of salvarsan and its derivatives.

Caution.—1. It should not be used at all, or used with caution in arterio-sclerosis where there is risk of sudden rise of blood-pressure.

2. In pulmonary or cerebral hæmorrhage there is risk of increasing the hæmorrhage.

3. In pulmonary œdema there is risk of increasing the œdema.

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Mode of administration.—*(a) By mouth.*—For local action in the mouth and stomach. It appears to be rapidly destroyed before it can enter the general circulation. Sometimes sublingual administration is resorted to for the production of systemic effects.

(b) Subcutaneously, when there may be a slight rise in blood-pressure; but a marked effect on the contracted bronchi; but owing to intense local vaso-constriction, it is very sparingly absorbed and a very small dose may not produce any systemic effect. Sometimes severe palpitation and muscular tremor may follow its use.

(c) Intramuscularly, causes rise in arterial pressure and relaxation of the bronchi.

(d) Intravenously, causes immediate and marked rise in arterial pressure. The best method in collapse and shock. The intravenous dose should be about $\frac{1}{50}$th of the hypodermic dose and should be given very slowly and freely diluted.

(e) Intracardially, in sudden failure of the heart (4-10 ms).

EXTRACTUM SUPRARENALI CORTICIS

Extract of Suprarenal Cortex

Syn.—Cortin.

An extract containing the specific principle of suprarenal cortex which, when injected, prolongs the life of cats or dogs from which the gland has been removed.

Dose.—1¼ to 2½ drs. or 5 to 10 mils.

Action and Uses

Suprarenal extract was first introduced for the cure of Addison's disease, the symptoms of which were believed to be due to absence of the internal secretion of the glands. It is now recognised that the cortical portion is associated with the production of this disease, and is necessary for the sustenance of life. Its removal is followed, after a few days, by extreme depression, increasing muscular weakness, passing into complete prostration terminating in death. In man its destruction or disease is followed by pigmentation of the skin, low blood-pressure, muscular weakness, vomiting and death—symptoms of Addison's disease. The basal metabolic rate is diminished to the extent of 25 p.c. The cortex is also intimately related to the sexual organs, and its over-activity inhibits the development of female sex glands. Women suffering from tumours of the cortex show signs of virilism, hirsutism and atrophy of the breast and uterus.

It is largely used in the treatment of **Addison's disease** which is associated with degenerative changes in the cortex, and it supplies the hormone absent in this disease. Its administration is followed by the disappearance of nearly all the signs and symptoms of the condition. The usual method of treatment is to give it subcutaneously, intramuscularly or by intravenous route 10 to 20 c.c. in divided doses daily.

It is also used in some forms of neurasthenia associated with low blood-pressure, low blood sugar and subnormal temperature.

EPHEDRINAE HYDROCHLORIDUM

Ephedrine Hydrochloride

Source.—The hydrochloride of an alkaloid, ephedrine, obtained from *Ephedra sinica, Ephedra equisetina*, and other species of ephedra.

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Characters.—Colourless crystals; odourless. *Soluble* in water and alcohol (90 p.c.). Aqueous solution neutral to litmus.
B.P. Dose.—$\frac{1}{4}$ to $1\frac{1}{2}$ grs. or 0.016 to 0.1 grm.

Non-official Preparations

1. **Elixir Ephedrinæ Hydrochloridi, B.P.C.**—Contains 1/4 gr. ephedrine hydrochloride in each dr. *Dose.*—1/2 to 2 dr. or 2 to 8 mils.
2. **Nebula Adrenalini et Ephedrinæ, B.P.C.**—Solution of adrenaline hydrochloride, 2 1/2 oz.; ephedrine hydrochloride 200 grs.; glycerin of phenol, 200 ms.; cinnamon water, q.s. 20 oz.

Pharmacology

The action of ephedrine resembles adrenaline, the effects being produced from stimulation of the sympathetic nerve-endings.

It is not absorbed by the unbroken skin, but is absorbed from mucous surfaces, stomach and rectum. The absorption however is slow and the effects last longer than adrenaline. It is a more stable compound, and its solution can be sterilised by boiling.

Eye.—A solution of ephedrine dropped into the eye causes slight mydriasis without affecting accommodation or increasing the intra-ocular tension, and producing little effect on the conjunctival vessels. All these effects are due to stimulation of the sympathetic myoneural junction, and is elicited by 1 to 5 p.c. solution.

Heart and circulation.—Administered by the mouth or hypodermically it stimulates the myoneural junctions of the sympathetic in the heart and the vaso-constrictors, but less powerfully than adrenaline, causing **acceleration of the**

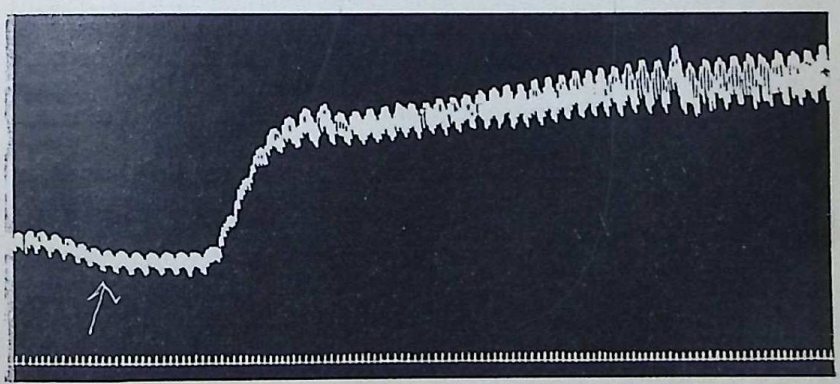

Fig.—5. Showing the effect of Ephedrine on Blood-pressure. Note the prolonged effect. Compare fig. 3 showing effect of adrenaline.
(Dog 4 kilo. 0.75 c c. of 0.3 p.c. ephedrine hydrochloride)

heart and rise of blood-pressure, which is more prolonged. The rate however becomes slow with the rise of pressure.

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The *heart muscles are directly depressed* but is not marked in ordinary doses, being overcome by the accelerator effect. In large doses the depression is marked. The rise of blood-pressure is not proportional to the dose and becomes less with successive doses, and eventually falls, possibly due to depression of the cardiac muscle (Chen).

Respiration.—It **stimulates the respiratory centre**, and relaxes the bronchial muscles specially when constricted as in asthma, or after physostigmine. This effect is due to its action on the broncho-dilator (sympathetic).

It stimulates the central nervous system, does not reduce the secretions, and stimulates the intestinal muscles which are depressed by adrenaline, although some observers report that its effect on the gut muscle is the same as adrenaline. The uterus contracts in all animals.

Therapeutics

Ephedrine is used in the same conditions where adrenaline is indicated. In **bronchial asthma** it gives relief within 20 to 30 minutes administered by the mouth in $\frac{1}{2}$ gr. doses, and given two to three times a day it will keep away the attacks. It is not so potent as adrenaline in severe attacks, and very soon toleration is induced, and a larger dose is required to produce the same result. Some patients complain of severe sweating and sleeplessness, while others show no effect after a single dose of $\frac{1}{2}$ gr.

It is used in anaphylactic shock, hay fever, urticaria and in angio-neurotic œdema, and as an addition to local anæsthetics in place of adrenaline. It counteracts the collapse which follows the use of spinal anæsthesia. In hay fever it acts both when given by the mouth and as a nasal spray (3 to 5 p.c.), when it causes immediate shrinkage of the engorged mucous membrane. This effect has been found useful in the treatment of cold and has been utilised in nasal surgery.

Because it stimulates the respiratory centre it is used in **narcotic poisoning**, and is superior to caffeine, strychnine, and even carbon dioxide (Chen).

It is useful in **nocturnal incontinence of urine** in children when given in $\frac{1}{2}$ gr. doses at bed-time to a child 10 to 12 years old; $\frac{1}{8}$ to $\frac{1}{4}$ gr. given twice a day to children 1 year old relieves **whooping cough**, specially during the second stage.

Its use has been recommended in complete **heart-block** and Gilchrist (*British Medical Journal*, April 7, 1934) used it in $\frac{1}{2}$ gr. doses in this condition with Stokes-Adams' syndrome three time a day. It relieves nerve pain in leprosy better than injections of adrenaline.

Toxic symptoms.—Large doses cause tachycardia, tremors, vertigo, palpitation, sweating, nausea and irritation of

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the bladder. They are associated with high blood-pressure and disappear when it returns to normal. The chief danger is cardiac depression and it should not be used in cardiac asthma, when the heart is damaged and in acute circulatory collapse.

Ephetonin. (Merck). *Syn.—Synthetic Ephedrine.*—A hydrochloride of *phenylmethylaminopropanol.* Closely related to ephedrine and has properties similar to ephedrine or adrenaline. Given orally in the same conditions where adrenaline is indicated. Supplied in tablets of ¾ gr. each and in ampoules for hypodermic injection.

2. Drugs Lowering the Blood-pressure

Vaso-dilators

Vaso-dilators are drugs which dilate the arterioles and lower the blood-pressure; they act in the following ways:—

1. *Depressing the vaso-motor centre.*—Narcotics, chloroform and ether anæsthesia.
2. *Depressing the sympathetic nerve cells.*—Nicotine, codeine, apocodeine.
3. *Depressing the plain muscles of the vessels.*—Nitrites, choline, theobromine.
4. *Paralysing the capillaries.*—Histamine, arsenic in poisonous doses.
5. *Depressing the vaso-motor nerve-endings.*—Ergotoxine in large doses.

AMYLIS NITRIS

Amyl Nitrite

Source.—Prepared by the esterification with nitrous acid of the fraction of fusel oil (which distils between 128° and 132°). Contains not less than 90 p.c. of nitrites, calculated as $C_5H_{11}O_2N$. Consists chiefly of the nitrites of *iso*-butyl carbinol, and *sec.* butylcarbinol, with other nitrites of the homologous series.

Characters.—A yellowish ethereal liquid; odour, fragrant; taste, pungent and aromatic; sp. gr. 0·874 to 0·884; *very volatile. Solubility.*—Soluble in alcohol (90 p.c.), insoluble in water.

Dispensing hints.—It should be kept in hermetically sealed bottles in a cool, dark place. Agitation or heat helps evaporation.

B.P. Dose.—2 to 5 ms. or 0·12 to 0·3 mil by inhalation.

Pharmacology

Externally.—Amyl nitrite is a direct local depressant to the sensory nerves, but the action is transitory.

Internally. **Blood.**—It enters the blood readily through the lungs and stomach, and circulates as sodium nitrite. If absorbed in sufficient quantity, it converts the hæmoglobin into methæmoglobin and another body—nitric oxide hæmoglobin—and renders the arterial and venous blood chocolate-coloured, and thereby interferes with the oxidising property of the corpuscles. In ordinary doses the effect is slight and the methæmoglobin is soon deoxidised, but in toxic doses these changes are enough to cause death. The inhalation of oxygen soon reconverts methæmoglobin.

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Heart and blood-vessels.—Within a minute of inhalation, face, head and neck become warm and flushed, the carotids and their branches throb, head feels full and tense, and the heart beats rapidly and violently, soon followed by headache, giddiness, rapid breathing and dilatation of the pupils. All these effects are due to dilatation of the vessels of the head and neck (blush area). But very soon the vessels of the whole body dilate with enormous fall of blood-pressure. These effects are due to direct action of the nitrite on the vessel walls and not to any effect on the vaso-motor centre, and the blood-pressure does not fall if the nitrite is introduced into the cerebral circulation and prevented from reaching the peripheral vessels. The dilatation is more marked in the splanchnic area and the extremities. The coronary, pulmonary and cerebral vessels also dilate, but the blood supply to the heart is reduced. The acceleration of the pulse-beat without any increase of its force is due to the depressed condition of the vagal centre, owing to the diminution of the blood-pressure. The heart muscle shows no important change, but the improved coronary circulation and lowered peripheral resistance may improve and relieve a weak heart.

Muscles.—The activity of most of the involuntary muscles is depressed, but the effect on arterial muscles is most marked. The muscles of the bronchioles, uterus and intestine also become relaxed.

Lungs.—Respiration is at first quickened by stimulation of the respiratory centre through diminished supply of blood to the brain as a result of the fall of blood-pressure. Later on it becomes laboured and difficult, and finally ceases altogether when the centre becomes asphyxiated. The bronchial muscles are relaxed.

Nervous system.—Most of the nervous symptoms such as headache, giddiness, throbbing in the head, etc., are due to the dilatation of the arterioles and fall of blood-pressure. In large doses reflex action is abolished owing to the profound paralysis of the motor centres in the cord. The function of the sensory and motor nerves are affected a few minutes before death.

Eye.—There is a temporary blurring of the sight as a result of the dilatation of the retinal vessels, dilatation of the pupil and increase of intra-ocular tension.

Temperature.—Under the influence of amyl nitrite the temperature falls both in health and fever, due to peripheral vascular dilatation, although the surface temperature may be increased from dilatation of the skin vessels.

Urine.—It escapes with the urine as nitrites and nitrates and is a feeble **diuretic** depending upon whether the renal vessels or those of the general circulation are relatively more dilated.

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THERAPEUTICS

Inhalation.—The profession first learned the use of amyl nitrite in **angina pectoris** from Brunton, who, seeing that it dilated the arterioles, used it in this disease with startling effects. Five drops give speedy relief, especially if the disease is paroxysmal. It may even afford relief to angina when there is no vaso-motor contraction. In fact, it relieves, though temporarily, any **cardiac pain** of a paroxysmal nature, but its action is of such fleeting nature as to render it useful only in emergency and should be followed during the interval of attacks by sodium nitrite or nitroglycerin. The pain of thoracic aneurism is often allayed by it. The "flushing" or "heat" which many women experience during the menopause may be controlled by this drug. It may arrest a fit of epilepsy if inhaled as soon as the aura is perceived. In migraine due to spasm of the blood-vessels of one side of the face, as indicated by the paleness of the affected side, inhalation of amyl nitrite gives relief. It has been found useful in **syncope** and **fainting.** Its use has been suggested in collapse of chloroform anæsthesia, but it should be remembered that in this condition the heart is extremely depressed and the arterial pressure is considerably low, and the use of amyl nitrite will lower the pressure still further which may be enough to stop the heart.

On account of its action in lowering blood-pressure its use has been advocated in **hæmoptysis** on the idea that it will help formation of clot at the point of injury, and in urgent cases we have often found it to give valuable results.

It has been found efficacious in uncomplicated **asthma,** relieving dyspnœa within a short time. It also temporarily affords relief to **cardiac dyspnœa** by lowering the pressure of the systemic arteries. It may relieve the pain of dysmenorrhœa and relax uterine spasms.

Caution.—It should be used with great caution in sensitive and nervous persons, who are powerfully affected by it. It should not be administered to persons suffering from aortic diseases, advanced degeneration of the cardiac muscle, those whose arteries are atheromatous, or to those who are emphysematous, plethoric or suffer from chronic bronchitis.

Prescribing hints.—Inhalation is the usual method. The drug may be poured on a handkerchief, or a glass ampoule broken within its folds and inhaled. The glass capsules keep better in India. Patients may become habituated to its use, so that after a while it has to be inhaled several times before it gives relief.

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TRINITROGLYCERIN

(*Not official*)

Syn.—Nitroglycerin; Trinitrin; Glonoin Oil; Nobel's Blasting Oil

Source.—By dropping glycerin into an ice-cold mixture of nitric and sulphuric acids: but the latter acid merely acts by absorbing the water which is given off.

Characters.—A colourless, oily liquid. Sp. gr. 1.6; slightly soluble in water, easily in fats, oil, alcohol and ether. Highly explosive. When mixed with silica it forms dynamite.

Composition.—It is a *Trinitrate of Glyceryl.*

Dose.—$\frac{1}{200}$ to $\frac{1}{80}$ gr. or 0·0003 to 0·0008 grm.

Official Preparations

1. **Liquor Glycerylis Trinitratis.** *Syn.*—*Solution of Nitroglycerin*; *Spiritus Glycerylis Nitratis.*—Contains $\frac{1}{60}$ gr. in 2 ms. **B.P. Dose.**—$\frac{1}{2}$ to 2 ms. or 0.03 to 0.12 mil.

2. **Tabella Glycerylis Trinitratis.** *Syn.*—*Tabellæ Trinitrini*; *Nitroglycerin Tablets.*—Each contains 0.0005 G. or $\frac{1}{120}$ gr. of Glyceryl trinitrate. **B.P. Dose.—1 or 2 tablets.**

ERYTHRITYLIS TETRANITRAS DILUTUS

Diluted Erythrityl Tetranitrate

Syn.—Erythrol Tetranitrate (50 p.c.).

Source.—A mixture of approximately equal weights of erthrityl tetranitrate and lactose.

Characters.—A white powder; odourless, tasteless, except for a slight sweet taste of lactose. Partially *soluble* in water, and in alcohol (90 p.c.).

B.P. Dose.—0.03 to 0.12 grm. (representing **0.015 to 0.06 grm.** of pure erythrityl tetranitrate); or **½ to 2 grs.** (representing ¼ to **1 gr.** of pure erythrityl tetranitrate).

Pharmacology and Therapeutics

Nitroglycerin is absorbed unaltered by the stomach, but on reaching the blood it is decomposed into glycerin, nitrites and nitrates. Its action is the same as that of amyl nitrite but the effects though not so prompt, are more lasting than those of amyl nitrite. For this reason, in the treatment of **angina pectoris**, nitroglycerin should be given in the intervals between the attacks with the object of curing the disease, whilst the inhalation of amyl nitrite should be reserved for the actual onset of the paroxysms. One of the drawbacks to the use of this drug is that it is apt to cause a severe throbbing headache. This may be avoided by breaking up each tablet into eight or more portions, and to take one of these portions every 15 or 20 minutes during the day. Patients rapidly become habituated to nitroglycerin.

Although it has no direct action on the heart its use has been advocated in different forms of cardiac diseases, and the benefit which follows its use is indirect due to vascular dilatation which decreases the resistance against which the

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left side of the heart is working. On the other hand its use is contra-indicated in advanced heart disease where the heart muscles are degenerated. Here the blood-pressure is already low and any further reduction of the pressure will not only lead to syncope from anæmia of the brain, but a low coronary pressure will also lessen the nutrition of the heart and still further weaken the muscle.

It is largely used for the purpose of lowering supernatural blood-pressure, but the general experience of clinicians is that the drugs of this group often fail to produce any permanent lowering of pressure.

It will often prevent sea-sickness, and if the treatment be commenced after sickness has already occurred, the patient may continue to vomit but the horrible feeling of nausea and depression disappear and the physiological effect of the drug does not occur. It must be given cautiously, and for administration to delicate persons or children the treatment should be commenced with a dose of $\frac{1}{200}$, $\frac{1}{400}$, or $\frac{1}{600}$ gr.

It is as a rule a perfectly safe drug and even children have taken large doses without ill effects.

Erythrol tetranitrate has a more prolonged action than amyl nitrite or nitroglycerin, but it is more expensive.

SODII NITRIS

Sodium Nitrite. $NaNO_2$

Source.—May be obtained by reducing sodium nitrate with metallic lead. Contains not less than 95 p.c. of pure sodium nitrite.

Characters.—Colourless, or slightly yellow, crystals, or a white, or slightly yellow granular powder. Taste, saline. Deliquescent. *Soluble* in 1·5 parts of water.

B.P. Dose.—$\frac{1}{2}$ to 2 grs. or 0·03 to 0·12 grm.

Pharmacology and Therapeutics

Sodium nitrite possesses properties similar to amyl nitrite and nitroglycerin, but it is slower in its action than the former and does not cause so much throbbing and headache as the latter. It is used in angina pectoris, aortic disease, and in the increased arterial tension which accompanies granular kidney. It has been used with success in hemicrania, and in bronchial asthma. In the air it gradually oxidises to nitrate and loses its efficacy. Given during the digestive period, *i.e.*, while there is free hydrochloric acid, it sets free nitrous acid, which is not only irritating to the stomach but may be partly oxidised and rendered inert before absorption.

For asthma, it is given combined with hyoscyamus in doses of 1 to 3 grs. frequently repeated.

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SPIRITUS AETHERIS NITROSI

Spirit of Nitrous Ether

Syn.—Sweet Spirit of Nitre. Sp. Æthylis Nitritis, U.S.P.

Source.—Obtained by distilling a mixture of alcohol (90 p.c.), nitric and sulphuric acids with copper; containing 1·25 to 2·5 p.c. w/v of ethyl nitrite.

Characters.—A transparent faintly yellow, inflammable liquid; odour penetrating apple-like; taste, characteristic; sp. gr. 0·838 to 0·842.

Incompatibles.—Potassium and other soluble iodides, iron sulphate, antipyrin, salicylates, tannic and gallic acids, tincture of guaiacum, and emulsions.

Dispensing hints.—It should be kept in small sealed amber bottles in the dark. A few crystals of potassium bicarbonate keep it neutral.

B.P. Dose.—15 to 60 ms. or 1 to 4 mils.

Pharmacology

Externally.—It causes a slight local anæsthesia by evaporation when applied to the skin.

Internally.—It possesses the combined properties of ether and nitrites which it contains, but in a milder degree. It is therefore a mild diffusible stimulant, antispasmodic and carminative.

Circulation.—It accelerates the cardiac activity and relaxes the peripheral blood-vessels, but not to such an extent as the nitrites. By dilating the renal and cutaneous vessels, it acts as a **diuretic** and **diaphoretic** respectively and acts as a mild **antipyretic.**

Elimination.—It is excreted by the kidneys and the lungs.

Therapeutics

Internally.—Spirit of nitrous ether forms one of the chief ingredients of a fever mixture. It is specially valuable in fevers during dentition of infants. As a **diuretic**, it is used in Bright's disease after the acute stage is passed. Dropsies of renal origin are reduced by its use, but it does little good in those of the cardiac type. One of the drawbacks to its use in children is that sometimes it has a nauseating effect.

GROUP VII

DRUGS ACTING ON THE RESPIRATORY SYSTEM

There is an intimate relation between the respiratory organs, the external air, the blood, the circulation, the nervous system and the respiratory centre. A disturbance in any one of them at once reflects upon the respiratory mechanism. The chief function of respiration is to supply oxygen to the tissues and excrete CO_2, and this oxygen

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requirement and CO_2 excretion are proportional to the degree of activity of the body. This gaseous exchange in the lungs and the tissues takes place according to the physical law of diffusion of gases, *i.e.*, the gas diffuses from a point of high tension to one of lower tension till equilibrium is established, when the diffusion becomes equal in both directions. Any failure of respiration is accompanied by deprivation of oxygen and accumulation of CO_2.

The complex process involved in respiratory movements is controlled by the *respiratory centre* situated in the pons and upper part of the medulla at the level of the calamus scriptorius. Although sensitive to various reflex stimulation, the centre is autonomous. It is possible that there are two centres, one normally concerned is the inspiratory centre which co-ordinates the inspiratory muscles concerned in the respiratory movements; the expiration being purely passive, the centre for expiration is not brought into activity except under special circumstances. The impulses of both inspiration and expiration for the entire respiratory mechanism are distributed in a co-ordinated way to the lower motor centres in the cord, and in the case of nose and larynx to the motor centres of the vagus and facial.

The vagus is the chief nerve of respiration, containing both sensory and motor fibres, and therefore plays a most important part in respiratory functions. The afferent filaments, which abundantly supply the wall of the air passages and probably the lungs, constantly transmit impressions to the centre and modify respiratory movements. Again, the muscles of the bronchi being supplied with the efferent fibres of the vagus, are constantly affected by various afferent impressions, which may even arise in the air tubes themselves. Besides the vagus there are other nerves which influence the respiratory movements.

The respiration is also influenced by variations in the blood-pressure. A rise in the pressure in the resting animal depresses respiration while a fall stimulates breathing. This effect is reflex, the rise of pressure stimulating the sensory endings in the aortic arch (supplied by the aortic branch of the vagus), and in the sinus caroticus (supplied by the sinus nerve, a branch of the glosso-pharyngeal).

Apart from the nervous control, the centre is highly sensitive to the conditions of the gases in the body. If the blood becomes more venous, the centre is stimulated and the respiratory movements augmented both in rate and force. Conversely, if the blood is more oxygenated by free ventilation of the lungs, or the tension of CO_2 is diminished, the centre acts more feebly, or may fail to act giving rise to a condition known as *apnœa*. The centre therefore is stimulated when the CO_2 tension of the plasma is increased. The CO_2 combines with water and forms carbonic acid, H_2CO_3.

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which dissociates to yield H-ion thus increasing the hydrogen-ion concentration of the blood which stimulates the centre. Respiration therefore is very sensitive to the slightest change in the hydrogen-ion concentration of the blood and responds in such a way as to keep the reaction at its normal level. Similarly after exercise a large amount of carbon dioxide is discharged into the plasma increasing its hydrogen-ion concentration which stimulates the respiratory centre resulting in augmented breathing, by which the excess of CO_2 is removed and more oxygen is absorbed to supply the muscles. Just as increased tension of carbon dioxide stimulates the centre so a lack of oxygen, though it does not directly stimulate the centre, makes it more sensitive to CO_2. If the deficiency of oxygen is not associated with increase of CO_2 the increased breathing will only eliminate more CO_2 thus reducing the hydrogen-ion concentration of the blood (alkalosis). Lack of oxygen is known as *anoxæmia*, and the symptoms develop as the supply of oxygen becomes deficient.

Drugs stimulating the respiratory centre.—We have already seen that alteration in the composition of the air inhaled and excess of carbon dioxide affect the respiratory centre. Any cause which tends to diminish the oxygenation of the blood, *e.g.*, hæmorrhage, or deficiency of hæmoglobin, as in anæmia or when brought about by certain drugs, stimulate the centre and increase the respiratory movements. In the same way iron, arsenic, and liver extract by increasing the hæmoglobin of the red blood-cells improve respiratory distress. The centre may be stimulated by certain drugs, specially strychnine, apomorphine, ammonia, caffeine, atropine, ephedrine, carbon dioxide gas, lobeline and camphor. Substances which stimulate the central nervous system also stimulate the respiratory centre. Finally the centre may be stimulated reflexly through sensory stimulation, *e.g.*, inspiration caused by application of cold to the body, inhalation of ammonia vapour or smelling salts.

Drugs depressing the respiratory centre.—The respiratory centre is more easily depressed than any of the other vital centres. In fact in most of the fatal diseases there is respiratory depression before death. Respiratory depressants make the centre less sensitive to carbon dioxide. Anæsthetics, hydrocyanic acid, aconite, gelsemium, etc., depress the centre. Morphine, heroin, chloral are powerful in this respect. The cough centre being closely related to the respiratory centre, respiratory depressants also depress the cough centre and are used to check excessive coughing.

The drugs belonging to this group are (*a*) *Respiratory stimulants*; (*b*) *expectorants*, or drugs which increase or liquefy the bronchial secretion and help its expulsion; (*c*) *bronchial antispasmodics*, or remedies which relieve respiratory spasms chiefly by relaxing the bronchial muscles; (*d*) *respiratory*

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sedatives, which allay cough and reduce excessive secretion, *e.g.*, opium and drugs of the belladonna group ; and (*e*) *pulmonary antiseptics*, or remedies which when inhaled, or when used internally, during excretion, act as antiseptics.

Class A : Carbon Dioxide. Oxygen

CARBONEI DIOXIDUM

Carbon Dioxide

Source.—May be obtained from mineral carbonates, or from the fermentation of sugars. For convenience it may be compressed in metal cylinders.

Characters.—A heavy, colourless gas. One volume of gas dissolves in about 13 volumes of water at 25° C.

Non-official Preparation

1. **Carbon Dioxide Snow.**—It is obtained by sudden release of liquid carbon dioxide contained in cylinders under a pressure of about 50 atmospheres. It has a temperature of -80°C. The solid snow is moulded into proper shape to suit the part which it is desired to treat. It is applied with slight pressure for from five to six seconds according to the effect desired. A short application of a few seconds causes blanching followed by hyperæmia, while prolonged application acts as a caustic like hot cautery and destroys diseased cells.

Pharmacology and Therapeutics

In the form of effervescent preparations CO_2 is extensively used in medicine, and many mineral waters and aerated waters contain CO_2 gas.

Locally applied, the gas or its solution, acts as a mild **irritant** to the skin and mucous membrane, and if the application is prolonged it is followed by **numbness** and **anæsthesia.** This sensory irritation leads to reflex stimulation. Carbon dioxide bath (Nauheim bath) is therefore used in many conditions of nervous and circulatory weakness, and in different diseases of the heart. Made into a pencil (carbon dioxide snow), it is used as a **mild caustic** for superficial growths, like warts, nævi, lupus, rodent ulcers, etc., in preference to other caustics.

Internally.—The same irritant effect is noticed when the gas is taken internally. In the stomach it improves appetite and acts as a **stomachic** by increasing its vascularity and secretion ; it also helps expulsion of gas and acts as a **carminative.** Aerated water is more quickly absorbed than ordinary water and having a sharp taste is more freely taken. It is therefore a valuable **diuretic** and can be used when rapid flushing of the system is desired. Being sedative to the stomach, aerated water, or carbonic acid gas in an effervescent mixture, may be used in vomiting, sea-sickness, etc.

Except when the gas is inhaled it produces no systemic effect taken by the mouth, being mostly expelled out from

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the stomach by eructation. Very little is absorbed and is excreted by the lungs, and does not alter the normal CO_2 content of the blood.

When inhaled in pure form, it causes asphyxia like any other indifferent gas, due partly to its effect on the central nervous system and partly to anoxæmia. Inhaled mixed with oxygen, it causes a rise of blood-pressure, first stimulates and then depresses the respiratory, vaso-motor and vagus centres. A concentration of 5 p.c. directly stimulates the respiratory centre. By stimulating the sensory nerve-endings in the carotid sinus region and the aortic arch, it sends excitory impulses to the respiratory centre so that CO_2 also stimulates the centre reflexly. The effects however disappear with the supply of fresh air. Stimulation generally follows the use of a concentration of $8\frac{1}{2}$ p.c., whereas a high concentration (20 to 30 p.c.) causes depression and paralysis of the vaso-motor centre and the heart. Normally, the respiration is regulated by the CO_2 content of the blood and the centre is sensitive to slight increase of CO_2 tension. Inhalation of oxygen with 5 p.c. CO_2 has therefore been used to **stimulate the respiration** and the vaso-motor centre in carbon monoxide poisoning, chloroform and ether anæsthesia and in narcotic poisoning. In chloroform and ether anæsthesia it stimulates breathing and accelerates absorption, thus hastens induction of anæsthesia; given after operation it ensures hyperventilation and deep breathing and thus helps elimination of the anæsthetic and diminishes the risk of post-anæsthetic complications, viz. nausea and bronchitis. It has been used successfully to control **hiccough** (30 p.c. of CO_2 to 70 p.c. of oxygen).

5 to 10 p.c. carbon dioxide in pure oxygen is a valuable means of raising the blood-pressure in spinal anæsthesia provided the motor nerves of respiration are not also paralysed, when artificial respiration and vaso-constrictor stimulants are of service.

It has been used in **asphyxia** of the new-born, **drowning**, and in **alcoholism** to hasten excretion by the lungs.

OXYGENIUM

Oxygen

Source.—Prepared by the fractional distillation of liquid air, or by the electrolysis of water. Contains not less than 96 p.c. v/v of O_2. For convenience it is compressed in metal cylinders.

Characters.—A colourless, odourless and tasteless gas. One volume dissolves in 43 volumes of water, and in 3.6 volumes of alcohol (95 p.c.).

Action and Uses

Oxygen, though present in small proportion (29.26 p.c.) as compared to nitrogen, is the most important constituent

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of air. An increase of this proportion or even inhalation of pure oxygen produces no noticeable effect under normal conditions, and the oxidation in the tissues is not increased nor metabolism modified, but tends to raise the blood-pressure and causes a slowing of the heart by causing sinus bradycardia. It has however a distinct value in cases where the tension of oxygen in the alveolar air is low or there is interference in the passage of oxygen through the alveolar wall, so that oxygen tension in the blood is below normal. At high altitudes the atmospheric oxygen tension is less and there is increased formation of red blood-cells and increased anabolism in other tissues specially the muscles.

The function of oxygen therapy is not to attack the underlying causes of the disease, but to give the patient the benefit of as high a blood oxygen saturation as possible. It is no doubt possible that some of the benefits of oxygen therapy may be obtained by other therapeutic measures apart from the improvement of arterial anoxæmia.

When hæmoglobin of the blood is so altered as to be incapable of carrying oxygen to the tissues, as for instance in poisoning by carbon monoxide, nitrites, chlorates, etc., inhalation of oxygen may be of some benefit. Similarly it is useful in those forms of **asphyxia** due to the interference with the access of oxygen to the blood, *e.g.*, in pneumonia, croup, drowning, etc. It is useful in anæmia where it increases the oxygen carried in solution by the plasma and not by increasing the quantity of oxygen carried by the hæmoglobin, in advanced heart disease when the supply of oxygen to the tissues is impaired from circulatory failure, and in respiratory failure and collapse in general anæsthesia.

It is of undoubted value in **coronary thrombosis**. A concentration of 50 p.c. will aid in maintaining an adequate oxygen supply to the tissues of the body until the heart has had an opportunity to recover from its functional disturbance.

Mode of administration.—For therapeutic purposes oxygen can be obtained in cylinders, and the simplest way is to pass the tube connected with the cylinder through water and then deliver through a glass funnel which is held near the patient's nose, or put into the mouth or into the nose by a rubber catheter with extra holes at the top. The catheter should be adjusted to the comfort of the patient and fixed in place with adhesive tape. Sometimes a large rubber bag is fixed in the tube to prevent the gas from issuing with too much force. In order that oxygen may be of any use, it is necessary that it should be given before any marked signs of cyanosis appear when giving to patients suffering from pneumonia. Ordinarily three bubbles a second when passed through water yield 0.2 litre per minute. When held before the nose much of the oxygen is wasted and the air becomes enriched by 3

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to 5 p.c. Subcutaneous injection is considered by French physicians as the route of choice, and it is claimed that when given by this method the effects are more pronounced, as a definite amount is supplied to the system promptly.

Method of subcutaneous injection.—In emergencies it can be supplied by connecting the outlet tube with a hypodermic needle, and introducing the gas into the tissues by pressing the rubber bag. This method is slow and the amount of oxygen introduced is uncertain. It may be introduced by a special apparatus. The outer aspect of the thigh or abdomen are the parts selected for injection. After the usual aseptic precautions, the needle is inserted through the skin and tissues between the fascia and the lower surface of the dermis, avoiding the subcutaneous fat as much as possible. Formation of an even swelling of tissue or of small bubbles appearing under the epidermis indicates satisfactory injection.

Amount to be injected.—Since oxygen is not toxic in any quantity, 5 to 6 litres may be injected without any difficulty. In bad cases of asphyxia 500 c.c. is quite suitable. Subcutaneous emphysema may appear and is of no consequence.

Class B : Expectorants

Expectorants are drugs which increase bronchial secretion and help its expulsion. To appreciate this action it is necessary to understand the natural mechanisms for protecting the air passages. They are *motor* and *secretory*. The motor mechanism consists of (1) propulsive movement of the cilia which line the mucous membrane; (2) reflex expulsive mechanism of cough; and (3) peristaltic movements of the muscles of the smaller bronchi. The secretory mechanism keeps the bronchial surface moist and dilutes irritating substances. The mucous membrane therefore is supplied with a large number of glands. Both these functions, *viz.* the motor and secretory, are regulated by the vagus and sympathetic nerves. The afferent fibres of the vagus transmit impulses from the mucous membrane, while the efferent fibres supply the muscles and the secretory glands. The muscles are also supplied by the efferent fibres of the sympathetic. Both these sets of fibres converge upon a hypothetical *cough centre* which is related to the respiratory and vomiting centres.

Gunn has classified expectorants as follows :—*

1. *Reflex expectorants.*—Most of the expectorants belong to this class. They act by stimulating the sensory ends of the vagus in the stomach and when given in large doses act as emetics. To this class belong tartar emetic, ipecacuanha,

* *British Medical Journal*, Vol. II. 1927.

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senega, quillaia, squill, ammonia, carbonate of ammonia, alkalies, apomorphine and camphor.

Similarly stimulation of the sensory endings of the vagus in the bronchial mucous membrane also increases bronchial secretion. Volatile oils, oleo-resins, balsams, etc., act in this way. These produce mild irritation during excretion through the bronchial mucous membrane.

2. *Central expectorants.*—To this class belongs apomorphine, which increases the secretion by stimulating the centre. Ipecacuanha and tartar emetic may have a central effect. The centre for bronchial secretion being closely associated with the vomiting centre in the medulla, emetics in small doses act as expectorants.

3. *Those acting by stimulating the secretory endings.*—Pilocarpine belongs to this group and acts by stimulating the parasympathetic endings.

4. *Those acting by stimulating the bronchial glands.*—Iodides increase secretion of the bronchial mucus by acting on the secreting cells during excretion. It was formerly believed that most expectorants, specially ammonium chloride and alkalies, acted by increasing the secretion of bronchial glands.

IPECACUANHA

Ipecacuanha

Syn.—Ipecacuanhæ Radix : Hippo.

Source.—The dried root of *Cephaelis Ipecacuanha*. Contains not less than 2 p.c. of the total alkaloids, calculated as *emetine*.

Characters.—Tortuous pieces, up to 15 cm. long, and 6 mm. thick, colour dark brick-red or brown, closely annulated. Fractured surface exhibits a wide, greyish bark and a dense central portion. Odour slight. Taste, bitter.

Composition.—Three alkaloids from 2 to 3 p.c., of this (1) *Emetine* 72 p.c. (2) *Cephaeline* 26 p.c. (3) A third alkaloid *Psychotrine* 2 p.c. (4) Methylpsychotrine and emetamine, present in small proportion. (5) Ipecacuanhic or cephaelic acid. (6) Starch, volatile oil, gum, etc.

Official Preparations

1. **Extractum Ipecacuanhæ Liquidum.**—Contains 2 p.c. w/v of the alkaloid emetine, or $\frac{1}{25}$ gr. in 2 ms. **B.P. Dose.**—$\frac{1}{2}$ to 2 ms. or 0.03 to 0.12 mil; 10 to 30 ms. or 0.6 to 2 mils, as emetic.

2. **Tinctura Ipecacuanhæ.**—Contains 0·1 p.c. w/v emetine, or $\frac{1}{30}$ gr. in 30 ms. **B.P. Dose.**—10 to 30 ms. or 0.6 to 2 mils; $\frac{1}{2}$ to 1 oz. or 15 to 30 mils, as emetic.

N.B. The tincture should be supplied when Vinum is ordered.

IPECACUANHA PULVERATA

Powdered Ipecacuanha

Syn.—Pulvis Ipecacuanhæ.

Source.—Ipecacuanha root reduced to a fine powder, and adjusted if necessary, by the addition of powdered lactose, to contain 2 p.c. of

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the total alkaloids, calculated as *emetine*. Contains $\frac{1}{25}$ gr. of emetine in 2 grs.

B.P. Dose.—$\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.; 15 to 30 grs. or 1 to 2 grm. as emetic.

Official Preparations

1. **Pulvis Ipecacuanhæ et Opii.** *Syn.*—*Pulvis Ipecacuanhæ Co.*; *Dover's Powder.*—Contains $\frac{1}{10}$ gr. morphine in 10 grs. **B.P. Dose.—5 to 10 grs. or 0.3. to 0.6 grm.**

2. **Trochiscus Morphinæ et Ipecacuanhæ.**—Contains $\frac{1}{32}$ gr. of morphine hydrochloride and $\frac{1}{10}$ gr. of ipecacuanha in each.

EMETINAE HYDROCHLORIDUM

Emetine Hydrochloride

Source.—The hydrochloride of an alkaloid, emetine, obtained from ipecacuanha root or prepared by the methylation of cephæline.

Characters.—Colourless, crystalline powder; odourless; taste, bitter. Soluble in water, and in alcohol (20 p.c.).

B.P. Dose.—$\frac{1}{2}$ to 1 gr. or 0.03 to 0.06 grm. by injection.

Official Preparation

1. **Emetinæ et Bismuthi Iodidum.**—A complex iodide of emetine and of bismuth. Prepared by precipitation from a solution of emetine hydrochloride by the addition of a solution of potassium bismuth iodide. Contains 25 to 28 p.c. emetine, and 18 to 21 p.c. of Bi. A reddish-orange powder. Odourless; taste, bitter, acrid. Insoluble in water. **B.P. Dose.—1 to 3 grs. or 0.06 to 0.2 grm.**

Non-official Preparations

1. **Linctus Ipecacuanhæ, B.P.C.**—Acet. Ipecac., Syrup of Tolu, Glycerin and Mucilage Tragacanth, equal parts. *Dose*—½ to 1 dr. or 2 to 4 mils.

2. **Syrupus Ipecacuanhæ, U. S. P.**—Fluid extract of Ipecacuanha 7, glycerin 10, syrup *q.s.* to 100. *Dose*, *U.S.P.*—Expectorant, 0.75 c.c. or 12 ms.; emetic, 15 c.c. or 4 drs.

3. **Emetine Periodide.** ($C_{29}H_{40}N_2O_4I$).—Introduced as a substitute for emetine-bismuth-iodide. Contains 38.7 p.c. of emetine. Can be given by the mouth without any local effect. Completely insoluble in weak acids. Dissolved and split up by weak alkalies. Supposed to be most effective and least toxic of all emetine preparations. Useful in refractory cases of amœbic dysentery. *Dose.*—2 grs. thrice daily after food for 15 days.

4. **Gavano.**—It is *mono-methyl ester of cephæline* in combination with an organic acid. Supposed to be of value in *chronic intestinal amœbiasis.* It can be taken by the mouth without nausea and vomiting, or any toxic effect on the heart. It is however not so effective in chronic cases as emetine-bismuth iodide or kurchi-bismuth iodide, but it is useful in acute cases specially where the liver is involved. *Dose.*—One tablet thrice daily for six days.

Pharmacology

Externally.—Powdered ipecacuanha acts as an irritant, rubefacient and pustulant on the unbroken skin. Emetine in 1 in 100,000 solution was thought to be destructive to amœbæ both pathogenic and non-pathogenic. But more recent observations have shown that a solution of 1 in 5000 kills amœbæ in broth cultures, while stronger solutions (1 in 100 to 1000) are required to destroy these organisms in bits

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of mucus freshly obtained from the intestine. It kills anthrax bacilli.

Internally. **Alimentary canal and liver.**—Ipecacuanha has an unpleasant bitter taste and excites the flow of saliva. In small doses ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) it increases the secretion of the gastric juice by stimulating the local circulation, and is therefore stomachic and tonic. In larger doses, 15 to 30 grs., it produces vomiting, by its direct influence on the peripheral ends of the vagus, hence it is a **direct emetic.** The vomiting is slow but certain and is unaccompanied by much nausea or prostration. It also acts as an emetic by acting on the centre in the medulla, but this effect is not observed in the ordinary methods of administration. In drop doses ipecacuanha tincture acts as an **antiemetic** in certain conditions. Emetine is a local irritant, and $\frac{1}{2}$ gr. given by the mouth causes nausea and vomiting followed by looseness and griping. The prolonged use of emetine induces diarrhœa, known as emetine diarrhœa. Given intravenously it is partly excreted by the intestinal mucosa, at the same time improves the tone and movement of the gut.

The liver is directly stimulated by the alkaloids of ipecacuanha and there is a plentiful secretion of bile.

Heart and circulation.—Emetine depresses the excitability and conductivity of the heart and slows the beat which

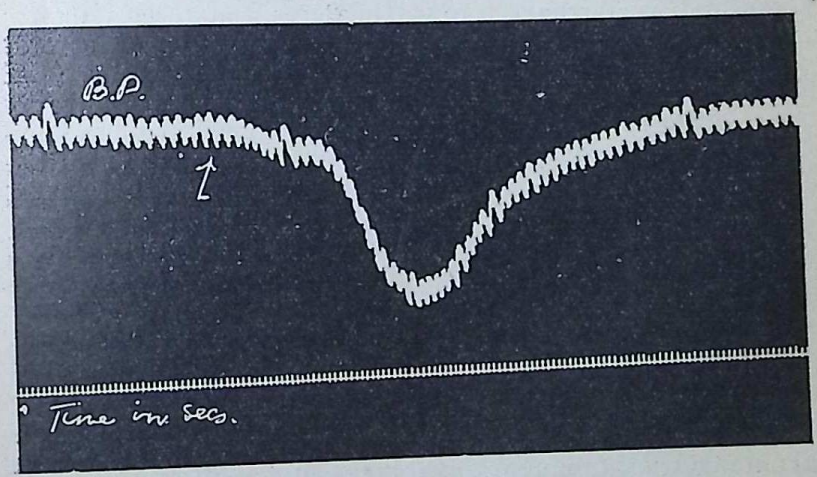

Fig.—6. Dog. Showing effect of Emetine on Blood-pressure. At the point of arrow 1 c.c. of a 0·1 p.c. solution was introduced into the femoral vein. Note the fall of pressure due to depression of the heart and dilatation of the vessels.

is not influenced by cutting the vagi or administration of atropine. The heart becomes irregular, auricular and ventricular dissociation may be induced and death may occur from auricular and ventricular fibrillation, the heart stopping in diastole. (Chopra and Ghosh). In toxic doses the heart

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becomes progressively slow and weak with fall of blood-pressure followed by collapse. These effects are more marked

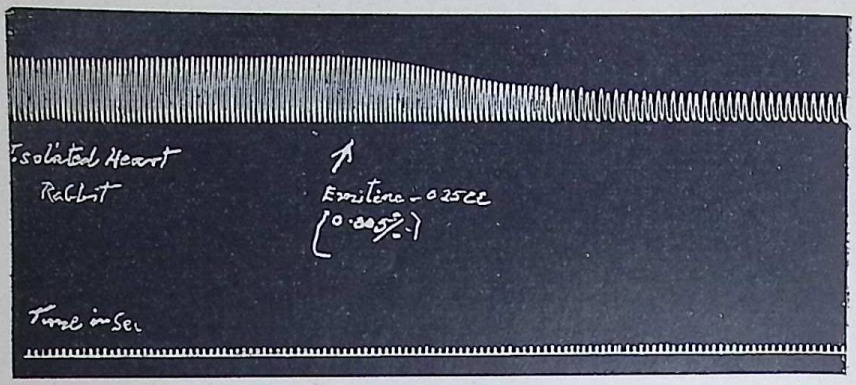

Fig. 7.—Tracing of the Movements of the Isolated Rabbit's Heart during Perfusion.

At the point of arrow 0·25 c.c. of 0.005 p.c. solution of emetine hydrochloride was introduced into the fluid. Note weakening and slowing of the heart. The force of systole getting weaker and weaker. Upstroke = systole.

when emetine is given intravenously. We have noticed tachycardia with giddiness following therapeutic doses of emetine. It is toxic to the capillary endothelium producing petechial hæmorrhage. In toxic doses the vessels dilate, while non-toxic doses given intravenously lower carotid pressure but increase pulmonary pressure.

Nervous system.—In frog it produces a slowly advancing central paralysis. In man there is a general depression producing weakness and lethargy, or there may be neuritis. In toxic doses there is degeneration of the anterior horn cells.

Respiratory tract.—It is an **expectorant** acting reflexly through the stomach. During elimination it also stimulates the bronchial mucous membrane and renders the secretion more fluid. Toxic doses of emetine have a tendency to pulmonary congestion, or to hæmorrhagic pneumonic consolidation.

Skin.—Moderate doses ($\frac{1}{2}$ to 1 gr.) stimulate the skin and produce **diaphoresis**, which action is increased by the combination with opium (Dover's powder).

Uterus.—It has been suggested that emetine should be avoided during pregnancy as it may cause abortion. Experiments with strips of rabbit's uterus have shown that emetine in dilutions of 1 in 150,000 to 1 in 100,000, the concentration attained after a dose of one grain in man, assuming that the whole of the alkaloid is in solution, has very little effect on the uterus. Since emetine does not produce contraction of the uterus it cannot be a factor in causing abortion, which is probably due to bacterial toxin and not to emetine.*

* R. N. Chopra and B. N. Ghosh, *Indian Medical Gazette*, 1922.

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Acute toxic action.—Emetine is cumulative. Severe diarrhœa, abdominal pain, tenesmus and toxic delirium have been reported from ½ gr. doses used for four days. Spehl and Collard noticed flaccid paralysis of the muscles of the neck with dysphagia and difficulty of mastication and speech, œdema of the face, and rapid, weak heart from 22 grs. given in 18 days. Acute renal insufficiency, general œdema, hæmoptysis, flaccid paralysis, peripheral neuritis, delirium, coma, and failure of the heart are the toxic symptoms.

THERAPEUTICS

Internally. **Alimentary canal.**—As a stomachic tonic, powdered ipecacuanha (¼ to ½ gr.) is used with other stomachics and bitters in atonic dyspepsia. Ipecacuanha tincture in 1 m. doses, every quarter to half hour, remarkably checks the **vomiting of pregnancy** and **gastric irritability** during febrile attacks and other diseases. In cases where it fails it may be given with ¼ minim of dilute hydrocyanic acid with good results. Ipecacuanha is not a suitable emetic in poisoning as its action is tardy, but it is exceedingly efficacious in **croup** and **bronchitis** of children, not only by mechanically expelling the mucus, but by its influence on the respiratory mucous membrane. 1 to 2 drs. of the tincture must be given every 1 or 2 hours until the child vomits. With some it merely acts as a purgative. It makes an excellent emetic in bilious attacks and in the early stage of fevers.

Powdered ipecacuanha in 20, 30 or even 60 or 90 grs. was used in the treatment of acute amœbic dysentery. To prevent its being rejected it was administered in keratin-coated pills, or an opium draught was given, or a hypodermic injection of morphine, an hour before the administration of the drug. Both in **acute hepatitis** and in **amœbic dysentery** the treatment by ipecacuanha *per os* has been replaced by the daily subcutaneous injection of emetine hydrochloride in doses varying from ¼ gr. to 1 gr., the most effective dose for adults being 1 gr. In effecting a cure co-operation of the host is necessary, and it is possible that the reticulo-endothelium system plays an important part (*see* page 65). In both these diseases pain, tenderness and fever in hepatitis, and blood, mucus and tenesmus in dysentery, rapidly disappear. Being, however, of no value in bacillary dysentery, it may be of value for purposes of differential diagnosis. It should be remembered that emetine is a cumulative and highly poisonous drug, and its prolonged use is followed by diarrhœa, lassitude, general weakness, paralysis of muscles, and feeble heart. The administration of the remedy should be stopped on the appearance of any of the toxic symptoms. In fact, not more than nine injections should be given in one course. In chronic forms with encysted amœbæ and in carriers, emetine-bismuth-iodide in

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keratin-coated pills should be given by the mouth. The only drawback is that it causes intense nausea and vomiting, and that hard tablets coated with keratin often pass out unchanged. In many chronic cases injection of emetine with oral use of Yatren (*q.v.*) gives better results. In subacute and chronic cases and diarrhœa, Dover's powder acts well. In pyorrhœa alveolaris emetine destroys the *Entamœba buccalis*, but since the amœba is not the cause of pyorrhœa it fails to cure.

It is also used in the treatment of **bilharziasis** with success, though not so efficacious as antimony. Since amœbic dysentery may also be a common complication of this disease, its use serves the double purpose, and it can be used in cases with advanced renal and hepatic disease or in those intolerant to antimony. It may be used *intravenously*, but in complicated cases should be used *intramuscularly*. The usual dose for intravenous use is 0.06 grm. the 1st day, 0.09 gm. 2nd day, and then 0.1 gm. on the 3rd, 5th, 7th, 9th, and 10th days with a total of 0.65-0.75 gm. It has also been recommended in **dracontiasis**.

Ipecacuanha is a most effective remedy for catarrhal jaundice and torpidity of the liver when given alone or combined with other cholagogues, and is a favourite constituent of aperient and cathartic pills.

Respiratory passages.—As an expectorant, ipecacuanha in the form of tincture, liquid extract, lozenge or syrup, is daily used in different inflammatory conditions of the respiratory passages, *e.g.* in cold, catarrh, acute and chronic bronchitis, and broncho-pneumonia. In these conditions it is used in smaller doses so as not to induce emesis. Ipecacuanha is also recommended in hay asthma and whooping cough. In acute pneumonia large doses have been given with success.

Emetine has been used in hæmoptysis, but clinical results are not very encouraging unless accompanied with a high blood-pressure; on the other hand there is risk of pulmonary congestion.

APOMORPHINAE HYDROCHLORIDUM

Apomorphine Hydrochloride. $C_{17}H_{17}NO_2,HCl,\frac{1}{2}H_2O$

Source.—The hydrochloride of an alkaloid apomorphine obtained from morphine by the abstraction of one molecule of water.

Characters.—Minute, glistening crystals: colourless or greyish-white, turning greenish on exposure to light and air; faintly acid. *Solubility.*—1 in 50 of water.

B.P. Dose.—$\frac{1}{60}$ to $\frac{1}{30}$ **gr. or 0.001 to 0.002 grm. as expectorant;** $\frac{1}{30}$ **to** $\frac{1}{8}$ **gr. or 0.002 to 0.008 grm. as emetic or hypnotic (subcutaneously).**

Non-official Preparations

1. **Syrupus Apomorphinæ, B.P.C.**—Apomorphine Hydrochloride 0.05, Acid Hydrochloric Dil, 0.25, Alcohol (90 p.c.) 4.5, Aqua 4.5, Syrup to 100. *Dose.*—½ to 1 dr. or 2 to 4 mils.

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2. **Linctus Apomorphinæ c. Codeina.**—Apomorphine 1/50 gr., Codeine Phosphate 1/12 gr., Acid Hydrocyanic Dil. 2 ms., Syrup of Virginian Prune to 1 dr. *Dose.*—1 dr. or 4 mils.

Pharmacology

Externally.—A 1 p.c. solution dropped into the eye causes anæsthesia but it may cause local pain and may induce vomiting from absorption.

Internally. **Stomach.**—Apomorphine is a reliable emetic acting directly on the vomiting centre. It acts within 10 to 15 minutes with the usual attendant symptoms of vomiting, *viz.* salivation, increased secretion from the nose, throat, and bronchial passages, and cold perspiration. These effects, however, are not due to any direct action of the drug on the stomach. It does not irritate the stomach, and produces emesis when other emetics given by the mouth fail. ⅓ gr. given per rectum also induces vomiting.

Heart and circulation.—In medicinal doses it has no action on the heart and blood-vessels, beyond a slight depression from the effect of vomiting, but in large doses it increases the frequency of the pulse, probably by stimulating the accelerator nerves.

Respiratory tract.—Unlike morphine, which in large doses depresses the respiratory centre, apomorphine in large doses stimulates the centre. Like all emetics, when given in small doses, apomorphine increases the secretion of bronchial mucus and makes it less viscid. This hypersecretion is also due to its direct influence on the cough centre. Very large doses paralyse the central nervous system, death takes place from respiratory failure although the heart continues to beat for some time.

Nervous system.—In large doses apomorphine produces excitement in animals which do not vomit. The respiration becomes quickened, but remains regular. In toxic doses there is ataxia and violent and irregular convulsions.

Therapeutics

Internally.—As a prompt and certain **emetic**, apomorphine is invaluable in poisoning, *i.e.*, in narcotic poisoning, drunkenness, etc. For this purpose 1/10 gr. hypodermically acts within 1 to 2 minutes; although given by the mouth it may produce vomiting after absorption, but large doses are necessary. A plum-stone obstructing the œsophagus was removed by vomiting induced by apomorphine. As an **expectorant**, it is always given by the mouth. In the early stage of the inflammation of the larynx, trachea and bronchi, when the mucous membrane is dry or secretes a viscid tenacious mucus, apomorphine loosens the secretion and removes inflammation. In croup and acute bronchitis of children it

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is useful. In subacute or chronic bronchitis, broncho-pneumonia, chronic catarrh of large tubes, or bronchial irritation caused by the inhalation of jute, flax, cotton or other foreign particles, it is most useful if the secretion is scanty and tenacious. In **whooping-cough** it has been found serviceable combined with morphine. Sometimes it can be usefully combined with morphine in the form of a linctus with syrup of wild cherry, syrup of tar or of lemon. It is valuable in persistent **hiccough.** One injection of $\frac{1}{10}$ gr. often gives permanent relief.

It is sometimes used in very small doses hypodermically as a sedative in **insomnia** without producing vomiting if the dose is not exceeded beyond $\frac{1}{32}$ gr. It has been used in alcoholic excitement and delirium tremens.

Caution.—It should be given with great caution to the feeble, the aged, and children, and to those subject to chronic diseases of the heart and lungs.

SENEGA

Senega

Source.—The dried root of *Polygala Senega.*

Characters.—Greyish or brownish-yellow, slender, from 5 to 20 cm. long, with a knotty crown bearing the bases of numerous slender aerial stems; frequently curved or contracted, sparingly branched, keeled, sometimes transversely wrinkled. Fracture, short. Odour, distinctive; taste, at first sweetish, afterwards acrid.

Composition.—It contains two glycosidal saponins, *viz.*, (1) *Senegin*, (2) *Polygalic acid*, which resemble, but are not identical with *quillaia-sapotoxin*, the active principle of *quillaja bark.*

B.P. Dose.—6 to 12 grs. or 0.4 to 0.8 grm.

Official Preparations

1. **Extractum Senegæ Liquidum.—B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**
2. **Tinctura Senegæ.—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**
3. **Infusum Senegæ Concentratum.—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.** Diluted with seven times its volume of water becomes equivalent to fresh infusion.
4. **Infusum Senegæ Recens.—B.P. Dose.—$\frac{1}{2}$ to 1 oz. or 15 to 30 mils.** Fresh infusion should be used within 12 hours of its preparation.

Pharmacology

The action of senega depends chiefly on the presence of senegin which resembles sapotoxin. These saponins form froth when shaken with water and emulsify oils and resinous substances. Sapotoxin is an irritant to the gastro-intestinal tract and causes nausea, salivation, vomiting and sometimes diarrhœa. Both quillaia and senega contain these saponins. They are mixtures of various generally colloidal substances of a glycosidal nature which produce much local irritation when used subcutaneously. They are not absorbed by the healthy epithelium of the alimentary tract and are decomposed by the

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alkalies and ferments into inert compounds. Introduced directly into the blood in large doses they cause convulsions and respiratory failure which may cause death. Small doses produce gastro-intestinal irritation with symptoms resembling dysentery. They are specially destructive to red blood cells and set free hæmoglobin into the serum. This effect is due to their affinity for cholesterin, and if they are saturated with cholesterin they lose this hæmolytic property.

When inhaled senega causes sneezing and cough. Taken by the mouth it acts as an expectorant, due chiefly to its nauseant effect. Senegin is excreted through the bronchial mucous membrane and during excretion increases the secretion.

It is eliminated by the skin and the kidneys, and while doing so stimulates their action moderately.

Therapeutics

The chief use of senega is as an **expectorant** in acute and chronic bronchitis and in pneumonia in the stage of resolution. It is of value in bronchiectasis. The best effects are obtained when senega is combined with ammonium carbonate.

Very small doses of senega (3 ms. of tincture to ½ oz.) emulsify fats and oils, and the tincture may be used with advantage in making the *Mistura Olei Ricini*.

QUILLAIA

Quillaia

Syn.—Quillaiæ Cortex; Panama Bark; Soap Bark.

Source.—The dried inner part of the bark of *Quillaja Saponaria* and other species of *Quillaja*.

Characters.—Flat pieces, 3 to 10 mm. thick, vary considerably in length and width. Outer surface brownish-white, or reddish-brown; inner surface smooth, white or yellowish-white. Taste, astringent, acrid. Powder irritates nostrils.

Composition.—(1) *Quillaja-sapotoxin* and (2) *Quillajic acid*, toxic glycosides, closely allied to saponin.

B.P. Dose.—1 to 3 grs. or 0.06 to 0.2 grm.

Enters into.—The preparation of Liq. Picis Carbonis and the

Official Preparation

1. **Tinctura Quillaiæ.—1 in 20. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Pharmacology and Therapeutics

Externally.—The powdered soap bark is very irritant to the nostrils, giving rise to a nasal discharge, sneezing, and sometimes cough, and its inhalation is therefore recommended in acute and chronic catarrhal rhinitis. It is a local stimulant to chronic ulcers and Shoemaker has been very successful in

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treating cases of this description by the application of bandages soaked in the infusion. It may be used for washing the skin and the scalp in the treatment of pediculosis.

Internally.—Quillaia bark contains five times more *saponin* or senegin than senega, and is therefore a more powerful expectorant. It may be given in chronic bronchitis, and emphysema with deficient expectoration, but its use is contra-indicated in hæmoptysis, or ulceration of the throat and alimentary canal, on account of its irritant properties. Because it contains a large percentage of saponin, it is largely employed for emulsifying insoluble drugs and oils.

Class C: Bronchial Antispasmodics

These drugs when used either as inhalation or by the mouth relieve respiratory spasm by relaxing the bronchial muscles. The bronchial muscles are supplied by the parasympathetic (vagus) which constricts, and sympathetic which dilates. Relaxation of the bronchial muscle is indicated in asthma. The spasm is relieved by atropine, hyoscine, lobeline etc., which depress the vagus endings; by adrenaline and ephedrine which stimulate the sympathetic nerve-endings; by nitrites and papaverine, which depress the muscle. Narcotics cause relaxation of the muscle by depressing the centre. Morphine, in small doses also causes relaxation of the bronchial muscles. Smoking of stramonium or datura cigarettes, or inhalation of smoke of nitre papers will often give temporary relief.

The Bronchial Antispasmodics are :—

Lobelia. Adrenaline (*see* page 277), **Ephedrine** (*see* page 282), **Atropine** (*see* page 227), **Nitrites** (*see* page 285), **Grindelia.**

LOBELIA

Lobelia

Source.—The dried aerial parts of *Lobelia inflata.*

Characters.—Stems, rounded, channelled, furnished with narrow wings: purplish hairy, scarred. Leaves irregularly toothed and hairy. Capsules, inflated, two-celled containing brown seeds. Odour irritating. Taste, at first slight, after chewing, burning and acrid.

Composition.—It contains (1) *Lobeline*, crystallises in broad colourless needles, (2) *Lobelanidine* in small irregular prisms, (3) *Lobelanine*, and a number of other alkaloids. (4) *Lobelic acid.*

B.P. Dose.—1 to 3 grs. or 0.06 to 0.2 grm.

Official Preparation

1. Tinctura Lobeliæ Ætherea.—1 in 5. B.P. Dose.—5 to 15 ms. or 0·3 to 1 mil.

Pharmacology

The action of lobelia is due to the presence of the alkaloid lobeline which resembles nicotine in its effects. It first

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stimulates and then depresses the parasympathetic ganglia. An injection of lobeline therefore causes increased salivary and bronchial secretions, constriction of the bronchial muscle, increased intestinal movements, slowing of the heart and a rise of blood-pressure. These effects however pass off soon and are followed by opposite effects.

Internally. **Gastro-intestinal canal.**—Whether absorbed by the skin or the stomach, lobelia in large doses, produces gastro-intestinal irritation, causing vomiting, purging and great prostration. The vomiting is probably due to the primary stimulation of the vomiting centre.

Heart and circulation.—The initial effect is slowing of the heart and a **fall of blood-pressure.** In cases of weak heart this effect may arrest it altogether. Usually however the heart returns to normal or there may be acceleration. These effects are due to the direct action on the muscle and on the vagus ganglia.

Respiration.—The bronchial muscles are relaxed and the effect is due to depression of the vagus endings or their ganglia. There may be an initial constriction from stimulation of the vagus ganglia. Lobeline lessens the CO_2 threshold and **stimulates the respiratory centre** causing considerable increase in pulmonary ventilation. It is therefore a respiratory stimulant.

Nervous system and muscles.—The convolutions are secondarily affected only by toxic doses, when coma, and sometimes convulsions, may occur. Besides its depressing effects on the cardiac, respiratory and vaso-motor centres, it lowers the activity of the motor centre of the cord, causing relaxation of muscles.

Therapeutics

For its powerful bronchial antispasmodic action it is very often used in **asthma.** Large doses sometimes cause great depression. If there is more or less dyspnœa throughout 24 hours the patient must have 10 ms. thrice daily, besides a few extra doses during the paroxysm. Often speedier relief is obtained by combining it with bromides, iodides, or morphine as in the following formula: Tr. Lobeliæ Ætheris dr. iii, Potassium Iodide, dr. ii; Pot. Bromide, dr. iii; Aqua chloroformi ad oz. viii. M. ft. Mist. $\frac{1}{12}$ part every two or three hours until relieved.

It is used in spasmodic bronchitis and whooping-cough, relieving the paroxysmal dyspnœa and spasms.

Because it stimulates the respiratory centre, lobeline is used in pneumonia, poisoning by carbon monoxide and morphine, and in the asphyxia of the new born. It may also be used in any case of *sudden respiratory failure* and may be combined with cardiac stimulants. The usual dose is $\frac{1}{20}$ gr.

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(3 mg.) hypodermically. It may be used intravenously in cases of extreme urgency, but since it produces other side effects specially on the heart, it should be used with caution in patients with weak myocardium.

GRINDELIA

Not official

Source.—Dried leaves and flowering tops of *Grindelia camporum.*

Characters.—Stems slender, yellow, smooth. Leaves 3 to 5 cm. long, oblong or spathulate, pale green, rigid, brittle, smooth glabrous; surface dotted; margin, coarsely serrate. All parts are more or less resinous. Odour balsamic. Taste, pungent, aromatic, bitter.

Composition.—(1) *Amorphous resins* (20 p c.). (2) *Hentriacontane,* a crystalline phytosterol, various glycerides, *l*-dextrose, tannin, colouring matter and a trace of volatile oil.

Non-official Preparation

1. **Extractum Grindeliæ Liquidum.**—1 in 1. *Dose.*—10 to 20 ms. or 0.6 to 1.2 mils.

Pharmacology

Internally.—It locally stimulates the stomach and acts as a mild stomachic, and if continued too long it may cause gastric uneasiness.

After absorption it slows the heart and respiration, but its chief action is on the bronchial mucous membrane which it stimulates, and on the muscular fibre of the bronchial tubes, which it relaxes. It is therefore an **expectorant** and a **bronchial antispasmodic.** In large doses it powerfully depresses the respiratory and cardiac centres, dilates the pupil and causes sleep. The cutaneous sensibility and reflex movements are lessened, and there is incomplete paralysis of the limbs.

Therapeutics

Internally.—Its chief use is in **asthma,** 20 or 30 ms. of the liquid extract given every half or one hour relieve a paroxysm after two, three or four doses. The dried leaves mixed with nitre may be burnt and the fumes inhaled with advantage. It has been found serviceable in spasmodic bronchitis, emphysema, whooping-cough and other spasmodic respiratory troubles.

Class D: Bronchial Sedatives

Persistent and ineffective cough, due to irritation of the throat or tenacious mucus, frequently gives trouble. Dry hacking cough is also common in phthisis. For relief of cough, belladonna, opium, heroin, codiene, dionin or wild cherry bark are indicated.

PRUNUS SEROTINA

Wild Cherry Bark

Syn.—Pruni Virginianæ Cortex.

Source.—The bark of *Prunus serotina,* collected in autumn.

Characters.—Curved or channelled pieces or irregular fragments, about 3 mm. thick. Young bark smooth, reddish-brown, marked with

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transversely elongated lenticels, and granular fracture. Old bark rough and nut-brown. Taste, astringent, aromatic and bitter. Odour after maceration with water, like bitter almonds.

Composition.—(1) *d-mandelonitrile glycoside* (*prunasin*) and (2) an *enzyme*. These two bodies yield hydrocyanic acid, *benzaldehyde* and dextrose in the presence of water. (3) A bitter principle, tannin, starch, resin, etc.

B.P. Dose.—15 to 30 grs. or 1 to 2 grm.

OFFICIAL PREPARATION

1. **Syrupus Pruni Serotinæ.** *Syn.—Syrupus Pruni Virginianæ.*— **B.P. Dose.—30 to 120 ms. or 2 to 8 mils.**

PHARMACOLOGY

Internally.—The wild cherry bark possesses very mild stomachic and tonic virtues, which are greatly antagonised by the tannin it contains. Its liquid preparations are sedative, because minute quantities of hydrocyanic acid are formed during the process of preparation.

THERAPEUTICS

Internally.—The syrup is used as a sweetening and flavouring agent in cough mixtures, but it can also allay cough in tea-spoonful doses, on account of its sedative virtues.

CLASS E: Pulmonary Antiseptics

Since certain antiseptics are elimininated in the breath, it has been supposed that their internal administration should have a lethal effect on microbes in the lungs, chiefly the tubercle bacillus. For this purpose these drugs are largely used in the treatment of pulmonary tuberculosis, and other septic conditions of the lungs. It must be borne in mind that during elimination they are considerably diluted, and do not reach the lungs in sufficient concentration to exert any destroying effect on the micro-organisms when administered *per os*. Used as an inhalation, they may have some beneficial effect in conditions characterised by offensive odour of the breath.

The pulmonary antiseptics are :—

Guaiacol, Creosote, Tar Preparations, Volatile Oils, mainly Oil of Siberian Fir, Oil of Eucalyptus, Terebene and Oil of Turpentine.

GUAIACOL

Guaiacol. $C_7H_8O_2$

Source.—May be prepared synthetically, or by the fractional distillation of wood-tar creosote.

Characters.—A colourless, oily, highly refractive liquid, or colourless crystals melting at 28°C. Odour, penetrating and smoky; taste, caustic. *Solubility.*—1 in 80 of water, freely in alcohol (90 p.c.), in ether, glycerin, and in fixed oils. Sp. gr. 1·116 to 1·125.

B.P. Dose.—5 to 10 ms. or 0·3 to 0·6 mil.

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CREOSOTUM

Creosote

Syn.—Creasote.

Source.—Obtained by the distillation of wood tar, and contains guaiacol, creosol and other phenols.

Characters.—A colourless or yellowish, highly refractive liquid; odour, penetrating and smoky; taste, acrid. *Solubility.*—Slightly soluble in water, miscible with alcohol (90 p.c.), ether, chloroform, fixed and volatile oils. Sp. gr. not below 1.070.

B.P. Dose.—2 to 10 ms. or 0·12 to 0·6 mil.

Non-official Preparations

1. **Creosoti Carbonas, U.S.P.** *Syn.—Creosotal.*—A viscid, amber-coloured almost odourless and tasteless liquid, insoluble in water, containing carbonates of guaiacol and creosol. *Dose, U.S.P.*—1 grm. or 15 grs.
2. **Vapor Creosoti Co.** *Syn.—Inhalatio Iodi Co.*—Creosote 2, Phenol 2, Tr. Iodine 1, Spt. Ether 1, Spt. Chloroform 2. Useful in tuberculosis, as inhalation from Yeo's inhaler.
3. **Guaiacol Benzoas.** *Syn.—Benzosol.*—In colourless, almost odourless and tasteless crystals. It is less nauseous. Useful in *incipient phthisis. Dose.*—3 to 10 grs. or 0.2 to 0.6 grm.
4. **Potassii Guaiacolsulphonas.** *Syn.—Thiocol.*—White powder soluble in water. Combines the good effects of creosote and guaiacol without their disadvantages. Especially useful for children. *Dose.*—7½ to 15 grs. or 0.5 to 1 grm.
5. **Guaiacol Camphorate.** *Syn.—Guaiacamphol.*—A combination of guaiacol and camphoric acid. For *night sweats of phthisis. Dose.*—5 to 10 grs. or 0.3 to 0.6 grm.
6. **Guaiacol Cinnamate.** *Syn.—Styracol.*—Insoluble in water. For *intestinal phthisis. Dose.*—5 to 15 grs. or 0.3 to 1 grm.
7. **Guaiacol Carbonate.** *Syn.—Duotal.*—An inodorous, tasteless powder. Insoluble in water. *Dose.*—5 to 15 grs. or 0.3 to 1 grm.

Pharmacology of Guaiacol and Creosote

Externally.—The action of creosote is very similar to that of carbolic acid, creosote being an **antiseptic, disinfectant** and **deodorant,** but as it is a complex product, its action is not always uniform, and cannot therefore be relied upon. Guaiacol is a local anæsthetic.

Internally. **Gastro-intestinal tract.**—When applied to the mouth, both creosote and guaiacol produce smarting and salivation, and destroy the epithelium. In the stomach they are supposed to depress the terminal filaments of the sensory nerves of the mucous membrane and to arrest putrefactive and fermentative processes by destroying low forms of vegetable life such as torulæ and sarcinæ without affecting the pepsin. Large doses cause nausea, vomiting, colic and diarrhœa, with frequent pulse and slow and laboured respiration, without producing any convulsion.

Guaiacol is an **antipyretic** and acts like the salicylates, and a powerful **diaphoretic.** 1 dr. mixed with olive oil or lanoline and rubbed over the skin causes profuse perspiration.

Secretions.—They are readily absorbed into the blood, and are eliminated by the bronchial mucous membrane and kidneys, which they stimulate, increasing the bronchial and urinary secretions, and if fetid removing their fœtor.

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Micro-organisms.—They act as poisons to microbes, especially to tubercle bacilli when locally brought into contact with them, as by inhalation.

THERAPEUTICS OF GUAIACOL AND CREOSOTE

Externally.—Like carbolic acid, creosote cannot be used as a general antiseptic on account of its indefinite composition. Creosote vapour or creosote spray is a useful inhalation in chronic bronchitis, phthisis, gangrene of the lungs, etc. A few drops of creosote or guaiacol rubbed on the pit of the stomach, the part being afterwards covered with cotton-wool, causes profuse diaphoresis, and will often bring down the temperature in cases of fever.

Internally. **Gastro-intestinal tract.**—A pellet of cotton-wool soaked in creosote or guaiacol relieves toothache when introduced into the cavity of the painful carious tooth. In small doses, 1 to 2 ms., they relieve nausea, vomiting and gastralgia. They also check fermentative dyspepsia and diarrhœa, when given with bismuth and alkalies. For internal use guaiacol is preferred.

Lungs.—Both creosote and guaiacol are considered specifics for **phthisis,** because of their supposed lethal effects on the tubercle bacilli. They must be commenced early and continued long and in increasing doses. Commencing with 5 to 10 ms. doses either may be increased up to 30 ms. Guaiacol carbonate and thiocol are better borne than creosote, and they may with advantage be combined with quinine. While some clinicians claim these remedies as valuable in relieving cough and expectoration and causing general improvement, others are equally sceptical and are of opinion that they are of little value. They often upset digestion when their use requires to be discontinued.

Prescribing hints.—Creosote or guaiacol may be given by mouth, in pilules, capsules, perles, emulsions or mixed with milk or cod-liver oil. Sometimes the mucus secretion of phthisis is wonderfully decreased by using the creosote spray. During hæmoptysis creosote treatment must be stopped. When combined with oxide of silver it forms an explosive compound unless previously mixed with some inert powder.

The creosote draught of the Victoria Park Hospital consists of Creosote 5 to 30 ms., Tinct. Gentianæ Co. 15 ms., Alcohol (90 p.c.) 15 ms., Ext. Glycyrrhizæ Liq. 30 ms., Water 1 oz.

For inhalation, creosote may either be given alone or mixed with phenol upon a respirator, or it may be used in the form of the Vapor Creosote. The Brompton formula is creosote 1, spirit of menthol (20 p.c.) 1, spirit of chloroform 1. The addition of spirit of chloroform makes it more sedative in its action.

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GROUP VIII

DRUGS ACTING ON THE GASTRO-INTESTINAL TRACT

Mouth.—Normally the mouth harbours a large number of bacteria, and although the majority of them are harmless saprophytes, under favourable conditions they are capable of developing pathogenic properties. Since many diseases arise from oral sepsis, the condition of the mouth is of great significance. Pyorrhœa alveolaris, infected tonsils and some forms of stomatitis have been known to produce diseases in some distant parts of the body. Oral sepsis is also a common cause of complication, through secondary infection, in diseases like typhoid, pneumonia, apoplexy, etc. A clean mouth therefore is of great importance in therapeutics. Unfortunately it is very difficult to keep the mouth sterile for more than a few minutes, although the use of disinfectants check the growth and further progress of the bacteria. The best means of keeping the mouth clean is by the use of dentifrices and antiseptic mouth washes so that food particles cannot lodge in between the teeth where they can undergo fermentation and decomposition. In case of septic condition of the mouth much can be done by cleaning the mouth with hydrogen peroxide ; tincture of iodine, either as paint or as a gargle diluted with warm water ; or by the systematic use of antiseptic tooth powder.

Treatment of pyorrhœa is unsatisfactory as it is very difficult to apply any disinfectant into the infected pockets. Attempts have been made to clip off the pockets and thus prevent accumulation of pus. Application of disinfectants by ionisation has been tried apparently with good result.

Dentifrices are preparations used for cleansing the teeth. They may be *antiseptic*, when they contain drugs like quinine, phenol, etc. ; and *astringent*, when they contain preparations containing tannin, like kino, krameria, myrobalans, etc.

Antiseptic mouth washes contain boric acid, phenol, thymol, potassium chlorate, etc. A useful preparation is *Liquor Antisepticus* which is an imitation of the proprietory preparation *Listerine* (*see* thymol). Hydrogen peroxide with water or tincture of iodine with water may also be used (*see* Gargles page 42).

Children often suffer from caries of the teeth, due either to acid-forming bacteria from decomposed food lodged between the teeth, or to deficiency of calcium in the system. Administration of cod-liver oil, or the use of food rich in vitamin D, with plenty of milk are indicated in cases of calcium deficiency. Normally whole milk supplies sufficient calcium and vitamin D. Butter, or liquor ergosterolis irradiati may also be administered to supply vitamin D.

Salivary secretion.—The saliva performs, two definite

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functions, *viz.*, (1) initiates the process of digestion and aids the deglutition of food; and (2) washes out of the mouth any harmful substances. The salivary glands are supplied by (1) *sympathetic*, stimulation of which causes vaso-constriction and a scanty flow of viscid saliva; and (2) the *parasympathetic*, stimulation of which causes vaso-dilatation and a copious flow of saliva.

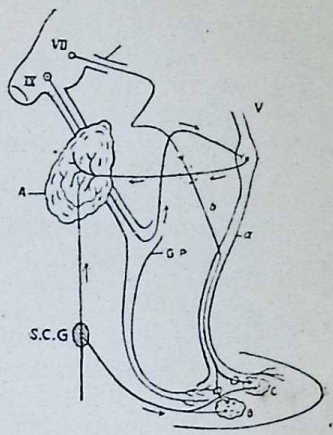

Fig. 8.—Innervation of the Salivary Glands. A, parotid; B, submaxillary; C, sublingual glands. s.c.g, superior cervical ganglion sending out sympathetic branches to the glands. *b*, chorda tympani (parasympathetic) supplying the submaxillary and the sublingual glands, through the facial. (After Mayer and Gottlieb).

Normally the secretion of saliva is increased by (*a*) the *psychic reflex*, excited by the sight or smell of food; (*b*) the *chemical stimulation* of the nerves of taste in the mouth, and (*c*) *mechanical stimulation* induced by chewing, this also provokes a flow of saliva chiefly from the parotid. The amount of saliva also depends upon the condition of the water content of the blood, *e.g.*, after profuse perspiration and excessive purgation the secretion is diminished and the mouth becomes dry.

Drugs which increase the secretion of saliva are called **sialagogues.** They may act as follows:—

1. *By exciting the periphery of the afferent nerves.*—These are acids and acid salts, pungents, aromatics, volatile oils, bitters, alcohol, ether, chloroform. They act reflexly from the mouth. Nauseants, like ipecacuanha and tartar emetic, act by stimulating the sensory ends of the vagus in the stomach.
2. *By stimulating the parasympathetic endings.*—These are sometimes called **specific sialagogues.** They are pilocarpine, choline, physostigmine and muscarine.
3. *By stimulating the ganglia.*—Nicotine.
4. *By stimulating the sympathetic endings.*—Adrenaline and ephedrine.

Many drugs, such as mercury and potassium iodide, are excreted with the saliva and increase its secretion. This is counteracted by atropine.

Drugs which decrease the secretion of saliva are called **antisialagogues.** They may act as follows:—

1. *By allaying irritation of the mouth*, as potassium chlorate, borax, astringent gargles, etc.
2. *By paralysing the parasympathetic endings.*—Atropine.

Opium and morphine also reduce salivary secretion by diminishing the excitability of the centres or sensory nerves.

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DRUGS ACTING ON THE STOMACH

The stomach forms the reservoir for the reception of food which it reduces to a liquid or semi-liquid condition partly by digestion and partly mechanically. The solid food remains in the stomach for several hours, and during this period the musculature contracts in such a way that the more liquid portions as they are formed are ejected at certain intervals through the pylorus into the duodenum. Except at definite intervals when the pyloric sphincter relaxes, the food is entirely shut off from the rest of the alimentary canal by the tonic contraction of both the pyloric and cardiac sphincters. The pyloric end protects the small intestine by preventing the passage of unassimilable material. This opening is under the control of reflex action, and is regulated by the degree of acidity of the stomach contents, and opens only when the food material has reached a certain stage of digestion. It also prevents concentrated solutions from entering the small intestine without being suitably diluted.

Two sets of nerves control the movements of the stomach, *viz.*, the *vagus* or *augmentor*, stimulation of which causes contraction, and the *splanchnics* or *inhibitor*, stimulation of which causes relaxation of the stomach and arrest of its movements, except the pyloric sphincter to which the fibres are motor. It is essentially an autonomic organ, gastric digestion may continue both as regards secretion and movements even after section of all the extrinsic nerves.

The gastric juice performs the following functions:—*

1. *Peptic digestion.*—This is helped by the secretion of pepsin and hydrochloric acid; and the most obvious function of the acid is to activate the pepsin to help the digestion of protein. This function however is not very important since the digestion of meat by the tryptic ferment remains unimpaired in the absence of hydrochloric acid.

2. *Antiseptic action.*—This is more important, as an acid secretion in the stomach kills many organisms, notably *streptococci*, which may be swallowed with food or carried from the mouth with saliva and other mucous secretions from the nose and pharynx. Moreover the dysentery, typhoid and cholera organisms are more or less killed by the gastric juice. Increased alkalinity of the contents of the small intestine, which results from the absence of hydrochloric acid in the stomach, favours the invasion of the duodenum, which is normally acid, with *B. coli* from the colon. The absence of hydrochloric acid therefore will favour infection of the small intestine with *streptococci* from above and with *B. coli* from below. These changes combined with the mechanical irritation of the mucous membrane with insufficiently broken down food will eventually lead to chronic enteritis.

* Hurst, *British Medical Journal*, *Oct.* 13, 1934.

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3. *Hæmopoiesis.*—(*a*) *Iron absorption.*—Normally the food contains sufficient iron for the maintenance of the normal percentage of hæmoglobin in the blood. In case of achlorhydria there may be deficiency of food and consequently of food iron, or if there be any loss of blood, the amount of iron absorbed from food may not be sufficient to maintain iron equilibrium, and microcytic anæmia may result. But how far this is due to failure of acid in converting the food iron into more assimilable form, or the inability of the intestine to absorb iron owing to unhealthy condition, is not settled.

(*b*) *Production of hæmopoietin.*—Castle has pointed out that the gastric juice contains a substance (intrinsic factor) which acts on the protein of the food (extrinsic factor) to produce a blood maturing principle essential for the maturation of the red blood corpuscles by the bone marrow, and its absence leads to Addisonian (pernicious) anæmia. This intrinsic factor which is of the nature of an enzyme has been named by Wilkinson as *hæmopoietin.*

4. *Production of Neuropoietin.*—It has recently been shown that the gastric juice also forms another substance allied to hæmopoietin which is essential for the normal nutrition of the central nervous system. It is also of the nature of an enzyme and its absence from the gastric juice leads to the degeneration of the posterior or the lateral columns of the spinal cord.

Gastric secretion is controlled by vagus which contains the secretory fibres. Stimulation of the peripheral end of the cut vagus is followed by secretion of the gastric juice. Pawlow and his followers have shown that the stomach of a hungry dog will secrete gastric juice if he saw or smelled food, though there was no food in the stomach, and this was possible as long as the vagi were intact. It is evident that sensation of taste, odour, etc., reflexly stimulates the secretory fibres of the vagus, and the secretion so induced is termed "*psychic or appetite secretion.*" This secretion initiates gastric digestion which is supplemented by further secretion arising in the stomach itself. It has therefore been suggested that this supplemental secretion is due to some chemical or hormonic stimulus. In fact Edkins (*Journal of Physiology*, 1906) has shown that extracts of pyloric mucous membrane when injected into the blood cause an increased secretion of gastric juice. This has been attributed to the formation of *secretagogues* produced by some food and which acting on the pyloric mucous membrane form *gastrin* or *gastric secretin*, which being carried through the blood, acts as a chemical stimulus to the glands. Some foods, chiefly meat extracts, soup, etc., provoke the formation of this chemical stimulus, while white of egg, bread, and isotonic salt solution produce no such action.

1. **Drugs which increase the secretion of gastric juice**

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are called stomachics.—They act by various means, *viz.* (1) *reflexly by stimulating the nerves of the mouth*, so-called *psychic secretion*. Substances which stimulate the gustatory endings of the mouth in an agreeable manner and which excite sensation of appetite, increase the secretion of gastric juice. To this class belong good food, condiments and wine. Bitters and aromatics before meals stimulate psychic secretion reflexly through the nerves of taste; (2) *by stimulating secretory fibres of the vagus*, pilocarpine and muscarine; (3) *direct stimulation of the fundus*. Pawlow has shown that alcohol in concentration of above 5 p.c. increases gastric secretion by stimulating the mucosa of the fundus; (4) *stimulation of the pylorus*, certain meat extracts, fatty acids, soups, etc., act as chemical stimulus, probably through hormonic action; (5) *alkalies*, which given before meals increase the quantity of gastric juice.

Subcutaneous injection of histamine (1 mg.) has been shown to increase gastric secretion. How it acts is not known. 0.5 to 1 mg. is used intramuscularly to differentiate true from pseudo achylia and also to test the secretory response of the stomach in gastric troubles.

2. **Drugs which decrease the secretion of gastric juice.**—Increased secretion of gastric juice or hyperchlorhydria may occur and requires treatment. The secretion is diminished by (1) *Astringents, e.g.*, salts of metals, opium, and substances containing tannin; these reduce vascularity and act as astringents; (2) *atropine*, which paralyses the vagus endings; (3) *fixed oils* and *fats;* (4) *alkalies*, these are largely used in certain forms of dyspepsia to neutralise excessive acidity due to lactic and fatty acids. The gastric juice is at first diminished but after recuperation the glands secrete more acid.

Just as peripheral stimulation increases psychic secretion, so also excitement, violent emotion and anxiety inhibit this secretion. Iced water will also diminish the secretion. Drinking iced water during or just before meals is therefore not desirable for proper digestion.

3. **Drugs modifying the composition of gastric juice.**—Gastric juice may be deficient, or may be excessive (hyperchlorhydria). Deficiency may be due to disease of the stomach, when less acid is secreted; or may be due to excessive accumulation of mucus, as happens in chronic gastritis. It is often absent or deficient in febrile conditions and many other diseases. Hyperchlorhydria is common in patients suffering from gastric ulcer. Excessive secretion is treated by alkalies. Of this magnesium oxide is best as it does not form carbonic acid which itself excites formation of gastric secretion. Calcium and magnesium carbonates come next. Bismuth carbonate is least powerful. To help digestion hydrochloric acid dilute is given alone or with pepsin.

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The deficiency of ferment is treated with such drugs as pepsin, pancreatin, papain and taka diastase.

4. **Drugs modifying gastric movements.**—Excessive movements of the stomach demand the use of drugs which have a soothing effect on the mucous membrane, or which will act through the motor mechanism. *Gastric sedatives* are drugs which soothe the mucous membrane of the stomach. They are cocaine, chlorbutol, or those which relieve vomiting (*see* antiemetics, page 326). Atropine and adrenaline reduce excessive movements, the former by depressing the vagus, the latter by stimulating the sympathetic. Opium diminishes gastric movements by acting on the muscle and causes contraction of the pyloric sphincter. Insoluble salts of bismuth, magnesium and calcium form protective coating and reduce gastric movements, while cocaine, hydrocyanic acid dilute, chlorbutol and chloroform depress the sensory endings and reduce reflex movements of the stomach.

The effect of acids and alkalies on gastric movements is of some practical value. The presence of free acid in the stomach causes closure of cardiac orifice, increases pyloric peristalsis and opens the pyloric sphincter and allows the gastric contents to enter the duodenum. The presence of free acid in the duodenum causes reflex closure of the pylorus which does not open till the contents have been neutralised by the intestinal juices. It will thus be seen that the control of the pyloric sphincter depends more upon the duodenum than on the stomach. Irritant solutions however cause closure of the pylorus, as happens when emetics are used, or when there are irritating food materials, when the stomach itself will reject by emesis, whereby the cardiac sphincter opens and the pyloric sphincter remains closed. Alkalies as a rule retard the emptying of the stomach, but the contents are emptied almost at the same rate when they are feebly alkaline or acid, or neutral.

5. **Drugs that help expulsion of gas, or carminatives.**—They act by (1) exciting regular peristaltic movements; (2) dilating either the cardiac or sometimes the pyloric sphincters; and (3) stimulating the nerves and muscles. The volatile oils are best in this respect. Aromatics and aromatic bitters, camphor, menthol, spirits, etc., are used to expel gas from the stomach.

Class A: Vegetable Bitters

The quality of bitterness is widely distributed throughout the vegetable kingdom, but many drugs, while possessing the bitter taste, have other and more important actions which overshadow the bitter quality, *e.g.*, nux vomica on the nervous system, and quinine as antiperiodic. On the other hand, bitterness is the only quality of the drugs of this group

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and their therapeutic uses are linked with this property. Bitters in this sense form a class of the larger group of *stomachics*.

Bitters are divided into :—

(*a*) *simple bitters*, like calumba, quassia, gentian, chirata ; and

(*b*) *aromatic bitters*. serpentary, aurantii cortex. The presence of volatile oil in this group materially adds to the stimulating effect.

CALUMBA

Calumba

Syn.—Calumbæ Radix.

Source.—The dried transversely or obliquely cut slices of the root of *Jateorhiza palmata*.

Characters.—In irregular, flattish, circular or oval, centrally depressed pieces : 2 to 6 cm. or more in diameter, 3 to 12 mm. in thickness ; yellowish. Cork, brownish, wrinkled ; cortex, thick with radiating lines.

Composition.—(1) *Columbin*, a colourless crystalline bitter principle. (2) Three yellow crystalline alkaloids, allied to berberine—*Columbamine*, *Palmatine* and *Jateorhizine*. (3) *Columbic acid*. (4) *Starch*. (5) *Mucilage*. No tannic acid.

B.P. Dose.—10 to 30 grs. or 0·6 to 2 grm.

Official Preparations

1. **Infusum Calumbæ Concentratum.**—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.
2. **Infusum Calumbæ Recens.**—Fresh infusion should be used within 12 hours of its preparation. B.P. Dose.—½ to 1 oz. or 15 to 30 mils.
3. **Tinctura Calumbæ.**—10 p.c. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.

QUASSIA

Quassia

Syn.—Quassiæ Lignum.

Source.—The wood of the trunk and branches of *Picræna excelsa*.

Characters.—Logs of varying length, or in chips or raspings ; yellowish white, tough, dense, but easily split. Inodorous. Taste, intensely bitter.

Composition.—(1) *Quassin*, a mixture of *α-picrasmin* and *β-picrasmin*, bitter principle. (2) A *volatile oil*.

B.P. Dose.—2 to 8 grs. or 0·12 to 0·5 grm.

Official Preparations

1. **Infusum Quassiæ Concentratum.**—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.
2. **Infusum Quassiæ Recens.**—B.P. Dose.—½ to 1 oz. or 15 to 30 mils. Should be used within 12 hours of its preparation.
3. **Tinctura Quassiæ.**—10 p.c. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.

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GENTIANA

Gentian

Syn.—Gentianæ Radix.

Source.—The dried rhizome, and root of *Gentiana lutea.*

Characters.—In yellowish-brown, entire or longitudinally split wrinkled cylindrical pieces, seldom exceeding 2½ cm. thick, varying in length, encircled by leaf-scar and terminated by a leaf-bud. Tough when moist, brittle when dried. Fractured surface reddish yellow. central portion soft, not radiate. Odour characteristic. Taste, first sweetish, then bitter. Should not yield *reactions with starch.*

Composition.—Contains two bitter principles, (1) *Gentiin* and (2) *Gentiamarin.* (3) A yellow crystalline phenol—*gentianic acid.* (4) A trisaccharide, *Gentianose*, pectin and *oil.*

Incompatibles.—Iron and lead salts, silver nitrate.

B.P. Dose.—10 to 30 grs. or 0·6 to 2 grm.

Official Preparations

1. **Extractum Gentianæ.**—B.P. Dose.—2 to 8 grs. or 0·12 to 0·5 grm.
2. **Infusum Gentianæ Compositum Concentratum.**—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.
3. **Infusum Gentianæ Compositum Recens.**—B.P. Dose.—¼ to 1 oz. or 15 to 30 mils.
4. **Tinctura Gentianæ Composita.**—1 in 10. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.

CHIRATA

Chiretta. (Not official)

Syn. I.V.—*Chireta*, Beng. *Chirayta*, Hind. *Bhunimba*, Sans.

Source.—The dried plant, *Swertia Chirata*, collected when in flower.

Characters.—*Stem*, about one metre long, smooth, brown, winged; branched above rounded below. *Root*, oblique. *Branches*, slender, decussate. *Leaves*, opposite, ovate, glabrous, entire. *Flowers*, small numerous panicled. *Fruits*, superior, bicarpellary, unilocular. No odour. Taste, extremely bitter.

Composition.—(1) *Chiratin*, an active amorphous bitter principle in combination with (2) *Ophelic Acid.* No tannic acid.

Non-official Preparations

1. **Infusum Chiratæ.**—1 in 20 (½ hour). *Dose.*—½ to 1 oz. or 15 to 30 mils.
2. **Tinctura Chiratæ.**—*Dose.*—½ to 1 dr. or 2 to 4 mils.

SERPENTARIA

Serpentary

Syn.—Serpentariæ Rhizoma.

Source.—The dried rhizome and roots of *Aristolochia reticulata*, known in commerce as Texan serpentary.

Characters.—Rhizome, tortuous, about 1 to 2 cm. long and about 2 mm. thick; the upper surface bearing remains of aerial stems up to about 2 mm. diameter; on the under surface numerous wiry roots about 10 cm. long and 0·2 to 1.2 mm. thick. Odour aromatic and camphoraceous; taste, strong, camphoraceous and bitter.

Composition.—A bitter principle apparently an alkaloid, a volatile oil 1 p.c. and tannin.

B.P. Dose.—¾ to 1½ gr. or 0.05 to 0.1 grm.

Enters into.—Tr. Cinchonæ Co.

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AURANTII CORTEX RECENS

Fresh Bitter-Orange Peel

Syn.—*Kamla nebur khosa*, Beng. *Narengi ke bokla*, Hind.

Source.—The fresh outer part of the pericarp of the ripe, or nearly ripe, fruit of *Citrus Aurantium*.

Characters.—Thin strips with but little of the white spongy part of the pericarp attached. Outer surface, red or deep orange-red and pitted. Epidermal cells, small and polygonal; parenchymatous tissue containing large oil glands and numerous crystals of calcium oxalate. Odour, fragrant; taste, aromatic and bitter.

Official Preparations

1. **Tinctura Aurantii.**—1 in 4. **B.P. Dose.**—30 to 60 ms. or 2 to 4 mils.
2. **Syrupus Aurantii.**—1 in 8. **B.P. Dose.**—30 to 120 ms. or 2 to 8 mils.

AURANTII CORTEX SICCATUS

Dried Bitter-Orange Peel

Source and characters.—The dried outer pericarp of the ripe, or nearly ripe fruit of *Citrus Aurantium*.

Composition.—(1) A *volatile oil*, 1 to 2 p.c., which consists of a terpene, dextro-rotatory limonene. (2) Three *glycosides*—hesperidin, iso-hesperidin, aurantiamarin, a bitter principle.

Enters into.—Inf. Gentianæ Co., Tr. Gentianæ Co., Tr. Cinchonæ Co.

Official Preparations

1. **Infusum Aurantii Concentratum.**—**B.P. Dose.**—30 to 60 ms. or 2 to 4 mils.
2. **Infusum Aurantii Recens.**—**B.P. Dose.**—½ to 1 oz. or 15 to 30 mils.

Pharmacology of Bitters

Internally. **Mouth.**—Pure bitters stimulate the nerves of taste and reflexly increase the salivary and gastric secretions.

Stomach and intestine.—Bitters have no action on the stomach, and introduced directly into the stomach through a tube cause no increase of gastric secretion. It is the bitter taste that determines the action and by some reflex path they stimulate the activity of the gastric glands. As a consequence the appetite is sharpened and digestion is improved. The gastric ferments are not increased although the increase of gastric juice augments the flow of pancreatic secretion. Bitters are used as stomachics and appetisers. Their efficacy is increased by combining with aromatics and alcoholic preparations. Large doses produce opposite effects, *i.e.*, diminish the secretion. If continued long they derange digestion by producing gastric catarrh.

In addition to the bitter property, aromatic bitters, because of the presence of volatile oils, act as carminatives and slightly increase the peristalsis.

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Blood.—Most bitters, like volatile oils, produce leucocytosis.

Therapeutics of Bitters

Bitters are daily used to promote appetite and digestion in cases where the stomach participates in the general enfeeblement of the functional activity caused by various diseases, overwork or starvation. They are specially valuable during the period of convalescence from acute diseases, but are contra-indicated in all diseases of the stomach that are accompanied by pain, vomiting, inflammation or ulceration, such as gastritis, gastrodynia, gastric ulcer, gastric cancer. An infusion may be injected into the rectum as an anthelmintic for thread-worms.

Prescribing hints.—Bitters should not be given in a concentrated form for a long time without interruption. Calumba is the least irritant of them all. Being free from tannin, calumba, quassia and chirata can be given with iron. They may be usefully combined with dilute hydrochloric or nitro-hydrochloric acids; or if there is any irritability of the stomach, with alkalies and bismuth salts. They are generally used 20 to 30 minutes before food. Quassia being devoid of flavour is intensely bitter.

Class B: Digestive Ferments

Pepsin, Pancreatin, Papain, Malt, Taka Diastase

1. Proteolytic Ferments

PEPSINUM

Pepsin

Source.—A proteolytic enzyme of the gastric juice of animals. Obtained from the mucous membrane of the stomach of certain animals commonly used as food.

Characters.—A colourless, or light buff-coloured, amorphous powder, or translucent scales; odour, faintly meaty; taste, slightly acid or saline. *Solubility.*—Moderately in water, and 1 in 100 of alcohol (90 p.c.). Should dissolve 2,500 times its weight of coagulated egg albumen.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Non-official Preparations

1. **Liquor Pepticus, B. P. C.**—Stronger glycerin of pepsin, 125 mils; dilute hydrochloric acid, 25 mils; alcohol (90 p.c.) 100 mils; glycerin, 25 mils; distilled water q.s. 1000 mils. *Dose.*—1 to 2 dr. or 4 to 8 mils.

2. **Mistura Bismuthi Composita cum Pepsino, B. P. C.**—1 dr. contains concentrated solution of bismuth ½ dr.; pepsin 1 gr.; tincture of nux vomica 7½ ms.; dilute hydrocyanic acid 2 ms, with chloroform, solution of bordeaux B and water. *Dose.*—½ to 1 dr. or 2 to 4 mils.

3. **Mistura Bismuthi Composita cum Pepsino et Morphina, B.P.C.**—Contains 1/40 gr. of morphine hydrochloride in 1 dr. of Mistura Bismuthi Co. cum Pepsino. *Dose.*—½ to 1 dr. or 2 to 4 mils.

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4. **Glycerinum Pepsini, B. P. C.**—Pepsin 100 G., hydrochloric acid 11.5 mils., glycerin 600 mils., water q.s. to 1000 mils. *Dose.*—1 to 2 dr. or 4 to 8 mils.

5. **Peptone.**—A product of digestion of albuminoid substances. Occurs in nearly odourless, white or yellowish-brown amorphous powder, or in scales, with a cheesy taste. *Dose.*—7½ grs. or 0·5 grm. twice daily an hour before meals.

6. **Seriparum, B. P. C.** *Syn.—Rennin, Rennet.*—An enzyme obtained from the glandular layer of the fourth or true digesting stomach of the calf having the property of coagulating or curdling milk. Milk that has been previously boiled will not coagulate with rennet, as the calcium salts have been precipitated by boiling. The essence is largely used for the preparation of junket, rennet whey, etc. 1 to 2 drs. will coagulate about a pint of milk.

7. **Pulvis Pepsini Compositus, B. P. C.**—Pepsin, about 1 in 6: pancreatin, 1 in 10; and diastase 1 in 100 with lactic acid, hydrochloric acid and lactose. *Dose.*—10 to 30 grs. or 0.6 to 2 grm.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Medicinal pepsin can convert outside the body in the presence of warmth, moisture and acidity, proteins (albumin, fibrin, etc.) into peptones, and this action is taken advantage of in predigesting food for administration by the mouth or rectum; but the taste of the peptonised product becomes so unpalatable that it cannot be ordinarily prescribed. As the rectum has very feeble digestive powers, peptone and peptonised food are used as nutrient enemata in a case of rectal feeding. But excepting glucose hardly anything else is absorbed by the rectum.

Internally.—A similar process within the stomach, as seen outside, takes place when pepsin is given by the mouth. It is therefore a valuable agent in helping the digestion of those in whom the secretion of the gastric juice is deficient from:

(1) Disease of the gastric follicles, as atrophy or dilatation.

(2) Excessive secretion of mucus, as chronic gastric catarrh, alcoholism.

(3) Deficient circulation, as in anæmia, general debility, old age.

(4) Irritable conditions of the stomach due to ulcer.

It is recommended in diarrhœa of children, and some forms of vomiting caused by imperfect digestion. It is useless for the digestion of carbohydrates and fatty food. Pepsin should, however, be used with judgment, for if continued too long it may lead to gastric atrophy. In fact most cases do well without any ferment. The gastric juice is more often deficient in hydrochloric acid, rarely the enzyme, and administration of dilute hydrochloric acid alone will help digestion by converting inactive pepsinogen into pepsin.

Peptone is used for non-specific desensitization in allergic conditions, and 0.5 grm. in cachets has been recommended an hour before meals in urticaria and migraine of gastro-intestinal origin which are instances of anaphylaxis. Injections of peptone once a week have been attended with good results in bronchial asthma by rendering the patient nonsensitive to protein. For intravenous use a 5 p.c. solution in normal saline is used. Begin with 5 ms. and increase with each dose by 2½

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ms. unless or until it produces too marked a general reaction. For intramuscular injection a 7.5 p.c. solution is used, commencing with 0.3 c.c. and increasing by 0.2 c.c. to a maximum of 1.5 c.c. which is reached at the 7th dose. These injections are given once or twice a week. Similarly intravenous injection of peptone is useful in various forms of infective fevers (*see* Protein Therapy).

Prescribing hints.—Pepsin may be given in powders, pills, cachets, tablets or capsules. Many of the market preparations are worthless. Being reliable preparations, glycerinum pepsini and Benger's liquor pepticus are the best to use. It should be given with, or directly after, meals, either combined with, or followed by, a dose of acid hydrochloric dilute.

PANCREATINUM

Pancreatin

Source.—A preparation of the pancreas, containing the enzymes, trypsin, amylase, and lipase. Prepared from the fresh pancreas of certain animals commonly employed as food, by extraction of one part with four parts of alcohol (25 p.c.).

Characters.—A colourless, or buff-colured, amorphous powder; odour meaty. *Soluble* in water, forming a slightly turbid solution; insoluble in alcohol (90 p.c.), and in ether. Should be kept in closed containers in a cool place.

B. P. Dose.—3 to 10 grs. or 0.2 to 0.6 grm.

Non-official Preparations

1. **Peptonised Milk.**—Dilute 1 pint of milk with 4 ozs. of water and heat to 130° F. (If a thermometer is not at hand, boil one-half of the mixture and add it to the other half). To this add two teaspoonfuls of liquor pancreatis or 5 grs. of extract pancreatis with 20 grs. sodium bicarbonate and leave the vessel near a fire or hearth for 15 minutes, or in the ordinary temperature of the room for 3 hours. If not used at once, it must be heated to boiling-point. Pulvis Pancreatini Co., containing both the extract and soda is more convenient.

2. **Pulvis Pancreatini Compositus, B. P. C.** *Syn.—Peptonising Powder.*—Pancreatin 20 mixed with sodium bicarbonate 80. In tubes of 25 grs., each of which is sufficient to peptonise one pint of milk.

3. **Liquor Pancreatini, B. P. C.** *Syn.—Liquor Pancreatis.*—Glycerin of pancreatin, about 1 in 6; with sodium bicarbonate, glycerin, alcohol (90 p.c.) and water. *Dose.*—½ to 2 dr. or 2 to 8 mils.

4. **Trypsin**—The proteolytic ferment of the pancreas. Converts proteins into peptones in alkaline media. Used for peptonising milk, and in *diabetes*. *Dose.*—3 to 10 grs. or 0·2 to 0·6 G. in keratin-coated pills.

5. **Injectio Trypsini Co. (Squire).**—A standardised liquid preparation. Contains a definite number of units of trypsin and amylopsin. *Dose.*—1 to 2 c.c., injected deeply daily into the buttocks, or healthy tissue in the neighbourhood of growths.

Pharmacology and Therapeutics

Internally.—Pancreatin or Pulvis Pancreatini Co. are best suited for predigesting liquid food before administration in dyspepsia, diarrhœa, and gastric troubles. Children deprived of natural nourishment fare well on pancreatised food. Trypsin and pancreatin, in pills coated with

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keratin, can be given two hours after meals with 20 grs. of sodium bicarbonate. Keratin protects them from the acid of the stomach, but it is doubtful whether the gastric juice becomes so deficient as not to exert any destructive effect on the pancreatic ferment. The value of pancreatic ferment is more problematical than that of pepsin. *Trypsogen*, which is supposed to contain enzymes of the islands of Langerhans is used in **diabetes** originating from pancreatic functional disturbance, but the results have not been satisfactory. Pancreatic emulsion is often given with cod-liver oil in wasting diseases when the stomach cannot well digest fat. Pancreatin has been used successfully as a preventive and for treatment of serum disease.

Trypsin has been used in the treatment of cancer, but has hitherto proved a failure. The hypodermic injection of sterilised trypsin solution is combined with its internal administration.

PAPAIN

(*Not official*)

Syn. I.V.—*Papyar ata*, Beng.
Source.—Prepared from the juice of the unripe fruit of papaw, *Carica Papaya.*
Characters.—A whitish, amorphous, slightly granular powder.
Dose.—2 to 10 grs. or 0.12 to 0.6 grm.

Non-official Preparations

1. **Elixir Papaini, B. P. C.**—Papain 5, alcohol (90 p.c.) 15, water 45, aromatic elixir to 100. *Dose.*—½ to 1 dr. or 2 to 4 mils with meals.
2. **Glycerinum Papaini, B. P. C.**—Papain 9, Hydrochloric Acid Dil. 8, Simple Elixir 5, Glycerin to 100. *Dose.*—½ to 1 dr. or 2 to 4 mils with meals.

Pharmacology and Therapeutics

Papain is used for the same purposes as pepsin and is very useful in cases where there are religious objections to the latter. It is also useful as a vermifuge for ascarides. Locally applied it causes absorption of diphtheritic exudations. The dry powder may be used, or it may be administered in the form of elixir or glycerin.

2. Amylolytic Ferments

EXTRACTUM MALTI

Extract of Malt

Source.—Prepared from sound malted grain of barley, *Hordeum distichon*, by digestion with water at a suitable temperature, and by evaporation of the strained liquid under reduced pressure at a temperature not exceeding 55°, until a viscous product is obtained. Contains nitrogen equivalent to not less than 4.5 p.c. w/w of protein.
Characters.—An amber or yellowish-brown, viscous liquid; odour, agreeable and characteristic; taste, sweet.
B.P. Dose.—60 to 240 ms. or 4 to 16 mils.

Official Preparation

1. **Extractum Malti c. Oleo Morrhuæ.**—Approximately 15 p.c. v/v cod-liver oil or 240 ms. contain 36 ms. of cod-liver oil. **B.P. Dose.—60 to 240 ms. or 4 to 16 mils.**

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Non-official Preparation

1. **Diastase.** *Syn.*—*Amylase.*—A mixture containing amylolytic enzymes obtained from an infusion of malt. Converts not less than 50 times its weight of potato starch into sugar. In yellowish-white, amorphous powder, or in translucent scales. Odourless and tasteless. *Dose.*—1 to 5 grs. or 0·06 to 0·3 grm.

Pharmacology and Therapeutics

The various malt extracts, either alone or combined with cod-liver oil, or irradiated to contain vitamin D are valuable as foods for persons suffering from *wasting diseases*, such as phthisis, as they are easily tolerated by the stomach, and maltose leads to the formation of fat. Malt is a good source of vitamin B.

Powdered malt in combination with baked wheaten flour in varying proportions forms most of the popular infant's foods. It may also be taken mixed with milk or beer or sprinkled over porridge, but as diastase only acts in an alkaline medium it is best to give malt two hours after a meal. It is doubtful if it exerts any appreciable effect in promoting carbohydrate digestion.

TAKA DIASTASE

(*Not official*)

Syn.—Koji.

Source.—An enzyme obtained from a species of *Eurotium Oryzæ*, cultivated on bran.

Characters.—A yellowish-white powder, which changes in a few minutes a hundred times its weight of starch into maltose.

Dose.—1 to 5 grs. or 0.06 to 0.3 grm.

Pharmacology and Therapeutics

It is very valuable in all forms of starchy dyspepsia with hyperacidity such as are common amongst the rice-eating inhabitants of Bengal, and it will be found *preferable to pepsin in all cases of this kind.* It may be combined like papain with sodium bicarbonate.

Class C: Emetics

Vomiting is a complex physiological phenomenon to produce which several parts are brought into play. The chief of them is the vomiting centre in the medulla and the afferent stimuli carried to the centre from various sources. The centre may be excited *directly* by disturbances in the cranial circulation (anæmia of the brain), or by mechanical and chemical stimuli, *e.g.*, pressure due to growth, meningitis, uræmia, etc.; or *indirectly* by certain peripheral stimuli, *e.g.*, various unpleasant sensations, repulsive sight, offensive smell, acute pain (renal colic), disturbances of the labyrinth (sea-sickness), and by certain drugs and poisons.

Emetics are drugs which produce vomiting. This is often accompanied by nausea, salivation, sweat, secretion of mucus

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from the air passages and œsophagus, quick pulse and irregular respiration. During the act of vomiting the cardiac sphincter opens and the pyloric portion of the stomach tightly contracts, and the contents of the stomach are expelled by a simultaneous contraction of the abdominal muscles and the diaphragm. The co-ordination of all these movements is controlled by the vomiting centre.

(1) *Local or Reflex Emetics*, also called *Gastric Emetics.*—These cause vomiting by stimulating the sensory endings of the vagus in the stomach. They act only when they reach the pyloric end of the stomach, and therefore act better when used with a large bulk of water for rapid action, as they then reach the pyloric end rapidly. They are often used in cases of poisoning, but being irritants they have an injurious effect if emesis does not occur. All gastric irritants act as emetics. Thus vomiting is a common accompaniment of almost all irritant poisons. The emetics are—zinc sulphate, alum, ipecacuanha, emetine, carbonate of ammonia, copper sulphate, tartar emetic, mustard, common salt, warm water.

(2) *Central Emetics.*—These act by stimulating the vomiting centre after absorption. As apomorphine.

Digitalis, morphine and lobeline also cause vomiting by stimulating the centre.

Therapeutics.—Emetics are used (1) to remove foreign bodies from the throat and œsophagus ; (2) to expel undigested substances and poisons from the stomach ; (3) to increase secretion of bronchial glands, in small doses ; and (4) sometimes to aid the action of antiperiodics.

They are *contra-indicated* in hernia, aneurism, prolapse of the rectum and uterus, peritoneal and intestinal inflammation, and in cases of threatened abortion, or where there is tendency to hæmorrhage or atheroma of vessels.

Class D : Antiemetics

These are drugs which are used to stop vomiting. They may act locally, when they are called *direct antiemetics*, or centrally. Examples of central vomiting are sea-sickness, vomiting of pregnancy, cyclic vomiting and vomiting due to passage of calculus through the ureter or bile duct. Prevention of central vomiting is rather difficult. Atropine counteracts the vomiting due to morphine and pyloric spasm. Bromides and chloral hydrate in large doses depress the centre. Amyl nitrite and nitroglycerin are sometimes useful. The common antiemetics are, small doses of adrenaline, alcohol, calomel and arsenious acid ; drop doses of solution of iodine or tincture of ipecacuanha ; hydrocyanic acid dilute, carbonic acid, cerium oxalate, cocaine, chlorbutol, creosote, ice, hot water and bismuth salts.

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ACIDUM HYDROCYANICUM DILUTUM

Dilute Hydrocyanic Acid. HCN

Syn.—Diluted Hydrogen Cyanide. Dilute Prussic Acid.

Source.—An aqueous solution containing 2 p.c. w/w of hydrogen cyanide; prepared by the interaction of dilute sulphuric acid and potassium ferrocyanide.

Characters.—A colourless, volatile liquid with peculiar odour; sp. gr. 0.997; faintly acid.

Incompatibles.—Copper, iron and silver salts, red mercuric oxide and sulphides.

B.P. Dose.—2 to 5 ms. or 0.12 to 0.3 mil.

Pharmacology

Externally.—Hydrocyanic acid is a protoplasmic poison, and is absorbed from the epidermis, but more readily from a raw surface. It paralyses the periphery of the sensory nerves, and thus acts as a **local sedative** and **anæsthetic.**

Internally. **Alimentary canal.**—It has an acrid bitter taste and causes burning and reflexly salivation followed by numbness in the mouth and throat. It is absorbed rapidly by the mucous membrane, and has the same action in the stomach as on the skin, *i.e.*, depresses the sensory nerve terminations. It is therefore a **gastric sedative** and relieves pain.

Blood.—It quickly enters the blood from all parts of the body and in poisoning it destroys the oxydase and prevents the cells from utilising the oxygen from the blood, consequently the oxyhæmoglobin is not reduced in capillaries, with the result that the venous blood is found scarlet red and the tissues suffer from oxygen starvation. If however death is delayed, or the dose is not lethal, the acid is changed to harmless products in the tissues, which enable the protoplasm to recover its oxygen-absorbing power; the expired air becomes less rich in oxygen and contains more carbonic acid, and the venous blood regains its usual dark purple colour.

Heart and blood-vessels.—A large dose at once arrests the heart in diastole, due to direct action on the cardiac centre, and the nervo-muscular apparatus of the heart, for it has been observed that hydrocyanic acid stops the heart's action even when topically applied. A small dose stimulates the vagal centre and **slows the pulse.** The blood pressure is first momentarily heightened and afterwards deeply lowered from a transitory stimulation and subsequent paralysis of the vaso-motor centre.

Respiration.—It is excreted by the bronchial mucous membrane and depresses the sensory endings thus acting as a sedative and reduces cough. The respiratory centre is paralysed after a brief stimulation. Respiration becomes feeble and laboured and death takes place from asphyxia,

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except in those cases where the heart is instantly stopped by a large dose.

Brain.—Medicinal doses have no action. Large doses cause insensibility and coma, referable either to the direct action of the drug on the cerebrum or to the altered conditions of blood from asphyxia. Pupils are dilated. Convulsions do not occur in man, but are common in animals.

Medulla and cord.—It is a paralyser of the respiratory, cardiac and vaso-motor centres. The reflex excitability of the cord is first lowered and then abolished altogether. The peripheral sensory nerves are less affected by internal administration than by local application. The motor nerves and muscles are also paralysed.

Elimination.—Hydrocyanic acid is rapidly excreted, chiefly by the breath. It is also partly changed to sulphocyanides, which are excreted in the urine.

Acute toxic action.—If the dose be large, it is followed almost instantaneously by a gasping cry, a few convulsive movements and death. But with a smaller dose, the patient becomes unconscious; his eyes fixed; pupils, dilated; pulse, feeble and irregular or imperceptible; respiration, slow, deep and convulsive with frothing at the mouth; skin, cold and clammy and at last death occurs. At the *post-mortem* are found the odour of hydrocyanic acid, lividity of the surface, clenched fingers, firmly closed jaws, froth at the mouth, fixed and glistening eyes, dilated pupils, dark blood, and slightly congested stomach.

Antidotes.—Emetics or pump if possible. Fresh air, cold and hot affusion alternately to the head, artificial respiration, diffusible stimulants, oxygen and ammonia inhalation, and electricity. Atropine and strychnine hypodermically. Protosalts of iron are chemical antidotes.

THERAPEUTICS

Externally.—Dilute hydrocyanic acid is rarely used now. It removes the itching of urticaria, lichen and dry eczema, when the affected parts are bathed or sponged with a lotion (2 drs. to 8 ozs. of rose water and glycerin). Care should always be taken not to apply the ointment or lotion to a raw surface.

Internally.—For irritative gastric disorders and dyspepsia it is ordinarily prescribed with sodium bicarbonate and bismuth as a gastric sedative. It is also used to stop vomiting of dyspepsia, gastric ulcer and of pregnancy in 1 to 2 ms. doses and to relieve the hacking cough of phthisis, and the spasms of hiccough. For this purpose it is generally used either in the form of syrup of wild cherry or tr. chloroformi et morphinæ co.

Prescribing hints.—For its sedative effect on the stomach, dilute hydrocyanic acid may be combined with sodium bicarbonate and given either as an effervescing draught, or combined with carbonates of bismuth and magnesium.

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CLASS E: Adsorbents

Charcoal, Kaolin (*see* page 127)

CARBO LIGNI

Wood Charcoal (Not official)

Source and chracters.—A black powder, free from grittiness, prepared by exposing wood to a red heat without access of air.

Dose.—1 to 2 drs. or 4 to 8 grms.

PHARMACOLOGY AND THERAPEUTICS

If we dissolve a dye in distilled water and pass it through finely powdered charcoal we find that most of the colour disappears. No chemical reaction has taken place, but the powdered charcoal has a large surface, and the action of this upon the dissolved particles of dye has made these accumulate or condense upon the surface of the charcoal by process of adsorption. This property is taken advantage of in the therapeutic uses of charcoal.

Externally.—Dry charcoal adsorbs and condenses gases within its interstices, specially oxygen, which it parts with to oxidise organic and other substances either liquid or gaseous. Hence it acts as a **disinfectant** and **deodorant.** It may, by giving off oxygen, help the growth of anaerobic organisms. In the same manner it adsorbs colloidal impurities, proteins, etc. The process of adsorption, being a surface action, is a purely physical phenomenon and the effect is greatest when the surface is very large, *i.e.*, the particles are very small, or the surface has been made greater by porosity.

Internally—It exerts the same adsorptive power in the stomach and intestine and therefore it is used in cases of poisoning by phosphorus, alkaloids, etc., and as it prevents the absorption of the poison its use should be followed by an aperient, preferably a saline, to expel the contents. Alone or combined with kaolin, which also acts in the same way, it is used in **diarrhœa, dysentery** and **cholera,** where it acts by checking bacterial growth and by adsorption of irritating putrefactive products.

Charcoal may be used in powder, cachets or lozenges either alone or combined with bismuth carbonate and betanaphthol in the treatment of flatulence and acid dyspepsia.

DRUGS ACTING ON THE INTESTINE

We have already seen that the acid chyme from the stomach enters the duodenum in driblets and Mellanby has shown that the presence of this liberates a hormone which excites the contraction of the gall-bladder so that a certain amount of bile enters the duodenum. The bile acids and their products of decomposition are partly absorbed and help the formation of secretin which stimulates both the pancreatic secretion and bile. Therefore the chyme is subjected to a further process of digestion by the secretion from the liver, the pancreas and the intestinal glands. The chyle and other soluble ingredients are absorbed by the lacteals and the portal veins as the chyme is propelled downwards by the intestinal movements.

Four kinds of movements, viz., *pendulum, rhythmic segmentation, peristaltic* and *vermiform,* occur in the intestine.

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The pendulum movements consist of rhythmic contraction and relaxation and is due to the spontaneous rhythmic action of the longitudinal muscle and takes place even in the isolated pieces of the gut. They move the contents backwards and forwards. Rhythmic segmentation helps to soften and mix the contents. It is essentially a series of local contraction of the circular muscle and occurs at those portions where the food mass is lodged, and is possibly due to local distention caused by the food. The peristaltic movements occur every three or four minutes and pass down the intestine carrying the contents downwards. They are excited reflexly by stretching and chemical stimuli. The vermiform movements are irregular and are confined to the colon.

Absorption is carried on by osmosis and diffusion, and excretion partly by osmosis and partly by the glands, which furnish the succus entericus. The excretion particularly of the watery portion is so profuse, that the effect of absorption is neutralised, and the contents of the small intestine and the duodenum remain liquid. In addition to this, certain micro-organisms, whose normal habitat is the intestinal tract, play an important part in the intestinal digestion. They may occasionally give rise to toxins and so produce symptoms of considerable gravity.

The absorption from the gut varies. Substances not soluble in water and lipoids are not absorbed at all, while the soluble ones are usually absorbed, though the lipoid-soluble substances more easily than the water-soluble ones. Absorption takes place from the small intestine, and the rate of absorption of water-soluble substances depends upon the rate of diffusion, which in its turn depends on the size of the molecules. True colloids like proteins and starch, are not absorbed, but soaps and alkaloids which are semi-colloids are rapidly absorbed.

The colon has a lower absorptive power than the small intestine. Sugar and salts are absorbed from the colon. Drugs that are absorbed by the intestine are as a rule absorbed when given per rectum, but more slowly. But substances which depend for their absorption upon the changes produced by the digestive juices are not absorbed when given per rectum. Many drugs however act quickly and strongly when administered per rectum.

The muscular coat is supplied by the sympathetic system through the splanchnic nerves, the stimulation of which causes inhibition and therefore arrest of movements, except the ileo-cæcal and the internal anal sphincters, and the muscularis mucosæ, to which the fibres are motor. The parasympathetic system supplies the motor or augmentor nerves, the stimulation of which causes increased peristalsis, but a strong stimulation induces vermiform contraction giving rise to colic. The peristaltic waves are controlled by the

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Auerbach's plexus. The vagus supplies the motor nerve to the whole of the intestine and also part of the colon, and the pelvic nerve supplies motor fibres to most of the colon and the rectum.

Intestinal Movements.—The intestinal movements are influenced by many drugs either through the nervous mechanism, through the muscle, or through irritation of the mucous membrane, *e.g.* irritant purgatives.

I. *The movements are increased by* (1) parasympathetic stimulation, *e.g.*, by pilocarpine, physostigmine, lobeline and choline. These act through the vagus endings independently of the Auerbach's plexus and the sympathetic apparatus. Choline being normally present in many tissues, it is generally believed that it assists in maintaining the activity of the gut. (2) Acting directly on the muscle, as pituitary extract, lead and barium salts and histamine. Rarely by digitalis and hormonal (extract of spleen). Strychnine acts on the muscle and by stimulating reflex excitability of Auerbach's plexus.

II. *The movements are diminished by* (1) nicotine, which stimulates the sympathetic ganglia; (2) adrenaline, stimulating the sympathetic endings; (3) atropine and hyoscine, by depressing the vagus (parasympathetic); (4) morphine, papaverine, benzyl benzoate, volatile oils and chloroform, by acting locally; and (5) bismuth salts, calcium and kaolin, by acting as mechanical protectives.

Violent and irregular intestinal movements occur in colic and are relieved by belladonna and opium. Belladonna is often combined with purgatives to check irregular movements of the gut and griping. In intestinal paresis pituitary extract and physostigmine are used subcutaneously. The movements are inhibited by anæsthetics or reflexly through the sympathetic. Any interference with the peritoneal cavity is followed by inhibition, as for instance postoperative paralysis of the intestine after abdominal operation.

Intestinal Antiseptics.—Since in most bacterial infections of the intestine the colon and the lower part of the small intestine are involved, intestinal disinfection implies disinfection of these parts. The seat of infection may be in the bowel wall itself, or the septic process may occur in the contents of the intestine. In either case the results have been disappointing and a drug strong enough to produce any bactericidal effect has an injurious action on the tissues of the gut. Intestinal antiseptics should possess the following qualities, viz.—(1) should be relatively non-toxic even if absorbed; (2) should act in an alkaline medium and in the presence of organic matter; (3) should not be destroyed in the upper part of the intestine and should have no injurious effect on the intestinal mucous membrane; and (4) should not interfere with the normal bacterial action of the intestinal mucosa. Such an ideal antiseptic is difficult to obtain

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and the so-called antiseptics have no such effect. In fact Schutz has shown that the healthy intestinal mucosa, which normally possesses germicidal action like other mucous membrane, becomes devoid of this property by the use of antiseptics and purgatives. Intestinal disinfection therefore is very difficult to produce, and it has been found almost impossible to cause even a diminution of the bacterial growth with certainty. Being slightly soluble, salol has often been used, which splits into phenol and salicylic acid in the gut. Salicylic acid, menthol, naphthol and thymol have been found effective experimentally. Fatty acid ester of thymol has been found effective in certain infections. Calomel is largely used as intestinal antiseptic; it acts not by any bactericidal action but by expelling the putrefying contents of the gut. Drugs which adsorb bacteria and toxins are sometimes more useful than many of the reputed intestinal disinfectants. Thus kaolin, which forms a coating on the whole of the intestinal mucosa, is used in the treatment of cholera and by its adsorbent effect prevents absorption of toxins. By irrigation of the colon with antiseptics some disinfection can be produced locally.

GROUP IX

PURGATIVES

Purgatives, Cathartics, Evacuants, or Aperients are drugs which cause evacuation of the bowels. The act of defæcation is accompanied by increased peristaltic contraction of the rectum and opening of the internal sphincter of the anus. It is not possible to definitely ascertain what normal impulse in the rectum produces the initial reflex for defæcation, possibly a certain amount of fullness and consistency of its contents form the necessary stimulus. Purgatives act either (*a*) by increasing the volume of the non-absorbable material; (*b*) by preventing the absorption of water; (*c*) by irritating the small and large intestine, and thus reflexly increasing peristalsis; and (*d*) by stimulating the neuro-muscular mechanism directly. The contents of the small intestine are poured out through the ileo-cæcal valve in an almost fluid condition, and the formation of the fæcal masses takes place during their long stay in the large intestine. A drug, therefore, which would simply increase the peristaltic movements of the intestine may give rise to watery evacuation by hurrying the contents into the rectum without giving time for absorption of the fluid; on the other hand the accumulation of a large quantity of fluid in the intestine reflexly excites peristalsis.

Many drugs cause looseness of the bowels, but since they act as powerful irritants they are not used as purgatives.

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An ideal purgative should not have any other effect except on the intestines, it should not irritate the stomach, but should become active only when it reaches the intestine. It should not be easily absorbed or absorbed so slowly that it can exert its effects throughout the intestine.

Some purgatives act mechanically, due to their bulk, and distending the bowel reflexly induce the need of evacuation. They are harmless and non-irritant and may be continued for a long time without any disadvantage. They are useful in habitual constipation and in cases where there is a deficiency of sufficient ballast to form the fæcal mass. Chief of these are agar-agar, cereals, liquid paraffin, ispaghula, Bael, etc.

Different purgatives act on different parts of the intestine. Castor oil, for instance, acts on the small intestine, having little or no effect on the colon. Aloes, senna and other anthracene purgatives act entirely on the large intestine without producing any effect on the movements of the stomach and small intestine. They, therefore, take longer time to act. The drastic purgatives increase the peristalsis of both the large and small intestines, and in large doses cause accumulation of fluid within the intestine.

Atony of the muscles of the intestine follows the use of most purgatives with consequent after-constipation. This effect is more marked after castor oil and rhubarb which contains rheo-tannic acid.

Some purgatives cause evacuation when given subcutaneously, while croton oil when rubbed on the skin also acts as a purgative. Senna, aloes and colocynth belong to the former group. But these effects are not due to any specific action on the bowel but in all probability result from their excretion into the intestine. Others again, not ordinarily used as purgatives, act as such when given subcutaneously by their special selective affinity on the nervous system or muscle. To this class belongs pilocarpine, choline, apocodeine and physostigmine. These act by stimulating the vagus endings. Pituitary extract acts on the muscle directly.

Therapeutics.—The purgatives are used (1) to remove fæcal accumulation in cases of constipation; (2) to drain serum from the blood in cases of cardiac, renal and hepatic dropsies; (3) to lower the temperature in fevers; (4) to lower the blood-pressure in apoplexy and cerebral congestion; (5) to prevent straining in persons suffering from piles, aneurism or hernia; (6) to expel bile and help the passage of biliary calculi; (7) to remove from the blood certain excrementitious matters, such as urea, uric acid, etc.; and (8) to remove irritating or otherwise harmful substances from the intestine, as in food poisoning, intestinal putrefaction, and in diarrhœa due to undigested food material.

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The purgatives are classified as follows :—

Class A : Those acting by selective affinity on the neuro-muscular apparatus **Pilocarpine, Physostigmine, Pituitary Extract, Choline, Apocodeine** and **Hormonal.** These drugs when given hypodermically stimulate the motor nerves or the muscle and act as purgatives.

Class B : Those acting by increasing the volume of non-absorbable material in the intestine

1. **Whole meal bread, Fruits, Oat Meal, Agar, Paraffin, Isuphgul** (*q.v.*), **Bael** (*q.v.*)
2. Saline purgatives : these act by interfering with absorption **Sulphate and Phosphate of Sodium, Acid Tartrate of Potassium, Sodium Potassium Tartrate, Sulphate, Carbonate and Oxide of Magnesium**

Class C : Those acting as irritants

1. Laxatives : **Tamarinds, Cassia, Manna, Castor Oil, Sulphur** (*q.v.*)
2. Anthracene purgatives : **Aloes, Rhubarb, Senna, Cascara, Phenolphthalein**
3. Drastic purgatives : **Scammony, Jalap, Croton Oil, Colocynth, Kaladana** (*q.v.*), **Turpeth** (*q v.*)
4. So-called cholagogue purgatives : There are really no cholagogues excepting bile and bile salts. All others simply act by hurrying the contents of the intestine by increasing peristalsis and thus preventing reabsorption of bile. They are—**Podophyllum, Euonymus, Iridin, Mercurials**

1. Saline Purgatives

POTASSII TARTRAS ACIDUS

Acid Potassium Tartrate. $KC_4H_5O_6$

Syn.—Purified Cream of Tartar ; Potassium Bitartrate.

Source.—Prepared from the crude cream of tartar which is deposited during the fermentation of grape juice. Contains not less than 99.5 p.c. of pure potassium hydrogen tartrate.

Characters.—In gritty, white crystalline powder, or colourless, opaque crystals. Taste, pleasant and acid. *Solubility.*—1 in 220 of water, not in alcohol (90 p.c.).

B. P. Dose.—15 to 60 grs. or 1 to 4 grms.

Enters into.—The preparation of Conf. Sulph., Pulv. Jalap. Co.

Non-official Preparation

1. **Potus Imperialis, B.P.C.** *Syn.—Imperial Drink.*—Acid. pot. tartrate 40 grs., citric acid 7 grs., sucrose 1 oz., oil of lemon 3 ms., tr. of lemon 50 ms., water q.s. 20 oz.

SODII ET POTASSII TARTRAS

Sodium Potassium Tartrate. $KNaC_4H_4O_6,4H_2O$

Syn.—Soda Tartarata ; Rochelle Salt ; Seignette's Salt.

Source.—Neutralise acid potassium tartrate with sodium carbonate. Contains not less than 99 p.c. pure sodium potassium tartrate.

Characters.—Colourless crystals, or a white crystalline powder ; taste, saline and cooling. *Soluble* in 1.5 parts of water, forming a clear, colourless solution ; almost insoluble in alcohol (90 p.c.).

B.P. Dose.—120 to 240 grs. or 8 to 16 grms.

Official Preparation

1. **Pulvis Effervescens Compositus.** *Syn.—Pulvis Sodæ Tartaratæ Effervescens ; Seidlitz Powder.*—Dissolve No. 1 powder in a tumbler of cold or warm water ; add No. 2 powder. To be taken while effervescing.

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SODII SULPHAS

Sodium Sulphate. $Na_2SO_4,10H_2O$

Syn.—Glauber's Salt.

Source.—Obtained by the interaction of sulphuric acid with sodium chloride.

Characters.—In colourless, odourless crystals; taste, bitter and saline. Efflorescent in dry air. *Soluble* in 3 parts of water, insoluble in alcohol (90 p.c.).

B.P. Dose.—30 to 240 grs. or 2 to 16 grms.

Official Preparation

1. **Sodii Sulphas Effervescens.—B.P. Dose.—60 to 240 grs. or 4 to 16 grms.**

Non-official Preparations

1. **Sodii Magnesii Sulphas Effervescens.**—Introduced by Martindale as a substitute for *Hunyadi Janos* and *Pullna waters*. *Dose.*—A teaspoonful or more, taken in half a tumbler of water half an hour before breakfast.

2. **Sal Carolinum Factitium, B.P.C.** *Syn.—Artificial Carlsbad Salt.*—Sodium Sulphate 55, Potassium Sulphate 1, Sodium Chloride 10, Sodium Carbonate 35. *Dose.*—30 to 60 grs. in warm water. 0.5 p.c. solution resembles *Carlsbad water*.

SODII PHOSPHAS

Sodium Phosphate. $Na_2HPO_4,12H_2O$

Syn.—Di-sodium Hydrogen Phosphate. Tasteless Purging Salt.

Source.—Prepared by the interaction of sodium carbonate and acid calcium phosphate. Contains not less than 99 p.c. of pure disodium hydrogen phosphate.

Characters.—Colourless, efflorescent, crystals. *Solubility.*—1 in 7 of cold water.

B.P. Dose.—30 to 240 grs. or 2 to 16 grms.

Official Preparation

1. **Sodii Phosphas Effervescens.—B.P. Dose.—60 to 240 grs. or 4 to 16 grms.**

SODII PHOSPHAS ACIDUS

Acid Sodium Phosphate. $NaH_2PO_4,2H_2O$

Syn.—Sodium Di-hydrogen Phosphate; Sodii Biphosphas, U.S.P.

Source.—Obtained by the combination of sodium phosphate with phosphoric acid. Contains not less than 98 p.c. of pure sodium di-hydrogen phosphate.

Characters.—Transparent, colourless, crystals, or a crystalline powder. Taste, saline and acid. *Soluble* in 1 part of water.

B.P. Dose.—30 to 60 grs. or 2 to 4 grms.

Pharmacology of Saline Purgatives

Under this head are included the sulphate and phosphate of sodium, the acid-tartrate of potassium, sodium potassium tartrate, and sulphate of magnesium, which, because of their low absorbability from the intestinal tract, disturb the osmotic balance between the bowel contents and the surrounding

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tissues. It has been found that certain salts are absorbed readily through the intestinal tract, and that this depends upon the nature of the ions of which they are composed. Among those that are absorbed very slowly are the cations, calcium, magnesium, and the heavy metals; and the anions, phosphates, sulphates, tartrates, citrates, etc. Of these magnesium among the basic, and citrates, phosphates, tartrates and sulphates among the acid ions have cathartic properties. When both ions are slowly absorbed the effect is more powerful, *e.g.*, magnesium sulphate is a stronger purgative than sodium sulphate, because the sodium ion is more easily absorbed than the magnesium ion, sulphate ion being common in both the salts. As a rule salines do not irritate the gut like the vegetable purgatives unless given in large doses. The action of saline purgatives is due not to irritation but to retarded absorption.

Solutions of these salts have an unpleasant salt taste, and when used in a concentrated form, they irritate the stomach and may produce nausea. If they remain longer they promote transudation and secretion and therefore help their own dilution. By means of a cæcal fistula it has been shown that if an isotonic salt solution and a solution of sodium sulphate be administered by the mouth, little or none of the former reaches the cæcum, while most of the latter solution escapes by the fistula, only about 10 to 20 p.c. being absorbed by the stomach and intestine. It is evident therefore that if any of the cathartic salts be used, from 80 to 90 p.c. of the fluid reaches the large intestine where it remains unabsorbed. The catharsis is due to the large bulk of the fluid which distends the bowel and induces increased peristalsis. The intensity of action of these salts depends upon the concentration of the solution in which they are administered. For instance, if the salt is freely diluted more of the fluid is absorbed and less reaches the large intestine. Whereas if the solution be hypertonic it will draw fluid from the blood into the intestine, due to its higher osmotic pressure, and the blood gives up its fluid without any sufficient compensation of salt until the solution becomes isotonic. A large amount of fluid thus accumulates with the resultant evacuation. Boas on the other hand asserts that the catharsis is less powerful when the solution used is more concentrated, and that the salt is more prone to be absorbed and to produce systemic effects. He reports several cases of poisoning from concentrated doses of magnesium sulphate. It must be borne in mind that purgation is produced only if the intestine is able to furnish a sufficiently large amount of fluid, which depends upon the amount of water present in the blood and tissues. It takes a longer time to produce purgation if a hypertonic solution is used, as its entrance into the duodenum causes closure of the pylorus, and the dilution results practically

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only from gradual secretion of the digestive juices. It may therefore take many hours before the quantity becomes large enough to produce an evacuation. A dilute solution on the other hand may cause a liquid stool, provided a large amount of it rapidly passes into the large bowel. If however there be no evacuation, the salt is absorbed into the blood and excreted by the kidneys and acts as a diuretic. MacCallum has suggested that salines act by precipitating calcium in the tissues and so neutralise its depressing action. The stool generally consists of

(1) the salt and the fluid derived by transudation, and

(2) some of the unabsorbed gastro-intestinal contents.

Bayliss and Starling have shown that the passage of liquids along the intestine is different from that of solid or pasty matter. Whereas solids stimulate peristalsis, liquids simply generate rhythmic intestinal segmentations; the result being that while the liquids pass along, more or less of the solid contents of the intestine are liable to be left behind. Hay has shown that when sulphate of magnesium is used for a long time it is excreted as sulphate in the urine in combination with sodium and potassium, thus reducing the alkali reserve of the body.

Therapeutics of Saline Purgatives

The saline purgatives are extensively used in cases of constipation, chiefly habitual constipation, as by increasing the fluidity of the intestinal contents they facilitate the expulsion of hard and dry fæces. They are however of little use in spastic constipation where drugs of the anthracene group are more useful. They are taken freely diluted in warm water, first thing in the morning, or the sulphate or the tartrate may be taken in the effervescing form. Sodium sulphate is the active principle of many natural mineral waters, e.g., *Carlsbad*, *Marienbad*, *Tarasp*, and *Condal* waters, while in combination with magnesium sulphate it occurs in *Aesculap*, *Hunyadi Janos*, *Pullna*, *Apenta* and *Kissingen waters*. *Friedrichshall* water contains sodium chloride in addition to the above mentioned ingredients. These mineral waters may be taken with advantage in chronic constipation. When a complete evacuation is required they are generally combined with some vegetable purgative, as pulvis jalap. co., mistura sennæ co. When we want to drain out fluid from the body as in dropsy, pleurisy, ascites, etc., salines are either used in concentrated solutions, or given with some drastic purgative like jalap, where the effect of the latter drug reinforces the hydragogue action. As these salines are not cleansing, it is customary to precede their use by a vegetable or mercurial purgative. The usual practice is to give a dose of calomel or blue pill at night and to

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follow it up in the morning with a dose of black draught, Seidlitz powder, Glauber's salt, Epsom salt, or some natural mineral water. Saline purgatives are extremely valuable in relieving portal congestion, and constipation associated with gout and uric acid diathesis.

Sulphate of soda is considered almost a specific in **bacillary dysentery**, and being less irritating than the sulphate of magnesium, is largely used in this disease. Sometimes the two salts are combined together. Epsom salt is an excellent purgative to counteract the constipating effect of iron in the treatment of anæmia.

In many cases the saline purgatives reduce the febrile temperature, and although they have no special action as intestinal antiseptics, they often reduce intestinal putrefaction by expelling the decomposing fæcal matter.

The different mineral waters are often used daily to reduce body weight and to lower **blood-pressure**. In the form of imperial drink the acid potassium tartrate is largely used by fever patients as a cooling and refreshing drink.

Sodium phosphate being mild and almost tasteless is suitable for a delicate stomach and for administration to children. Acid sodium phosphate being the natural acid of the urine, is largely used to render the alkaline urine acid in 30 gr. doses. It is successfully used in the treatment of oxaluria and cystitis, particularly when due to B. coli infection.

2. Laxatives

AGAR

Agar

Syn.—Agar-agar.

Source.—A dried gelatinous substance obtained from *Gelidium corneum*, *G. cartilagineum*, and other closely allied Rhodophyceæ.

Characters.—In slender, translucent, nearly colourless, lustrous strips, 4 millimetres wide, or flattened yellowish bands about 4 centimetres wide; or a greyish-white powder; swells to a gelatinous mass when immersed in water. *Insoluble* in cold water, soluble in 100 parts of boiling water which forms a stiff jelly on cooling.

B.P. Dose.—60 to 240 grs. or 4 to 16 grms.

Pharmacology and Therapeutics

Agar is largely used for preparing culture media for bacteriological purposes. It is tasteless, and when boiled with water or milk (1 in 200) forms into a jelly which may be given to invalids as food. Given internally mixed with milk, fruits or any other vehicle it is not absorbed by the digestive juices and passes through the intestinal canal almost unchanged, only about 8 to 27 p.c. being utilised. During its passage through the gut it draws moisture and increases in bulk which stimulates peristalsis and acts as a

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mild laxative, making the stools soft and bulky. It is valuable in habitual constipation, and may be combined with liquid paraffin or cascara.

TAMARINDUS

Tamarinds

Source.—Consists of the fruits of *Tamarindus indica,* freed from the brittle outer part of the pericarp, and preserved with sugar.

Characters.—A reddish-brown, moist, sugary mass, containing strong fibres, and brown shining seeds, each enclosed in a membranous coat. Taste, agreeable acid; odour, fragrant and fruity.

Composition.—(1) *Tartaric acid,* 10 p.c. and *acid potassium tartrate,* 8 p.c. (2) *Citric, acetic* and other acids. (3) *Invert sugar,* 25 to 40 p.c.

Enters into.—Confectio sennæ.

Pharmacology and Therapeutics

As a refrigerant, tamarind whey (tamarind 1, milk 30) is given as a drink in fevers. It is a mild laxative, and when spread on bread and butter forms a pleasant purgative for children.

CASSIAE

Cassia

Syn.—Cassiæ Pulpa.

Syn. I.V.—*Sondaler ata,* Beng. *Amaltas,* Hind.

Source.—The pulp obtained from the *Cassia Pods* by percolation with water, and evaporation on a water-bath to the consistence of a soft extract.

Composition.—(1) A *Purgative principle* allied to cathartic acid. (2) *Sugar,* about 50 p.c.

B.P. Dose.—60 to 120 grs. or 4 to 8 grm.

Uses.—Cassia pulp is never given alone on account of its griping properties, but with senna in the form of confection of senna.

MANNA, U.S.P.

(*Not official*)

The dried saccharine exudation of an ash-tree, *Fraxinus Ornus.* Contains 90 p.c. mannite. Yields not less than 75 p.c. of anhydrous alcohol soluble extractive when extracted with boiling 90 p.c. alcohol by volume.

Dose. U.S.P.—15 grm. or 4 dr.

Manna is a mild laxative by virtue of its sugar. It is largely used for children and delicate women, in hot milk, or in combination with other purgatives.

OLEUM RICINI

Castor Oil

Syn. I.V.—*Bheranda Tel,* Beng. *Arand Tel, Rendi Tel,* Hind.

Source.—The oil expressed from the seeds of *Ricinus communis.*

Characters.—Viscid, nearly colourless, or faintly yellow. Odour, faint; taste, bland at first, acrid and unpleasant afterwards. Sp. gr. 0.958 to 0.969. *Solubility.*—1 in 3½ of alcohol (90 p.c.).

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Characters of the seeds.—Oval, compressed, shining, marbled with reddish-brown or black-brown spots or stripes. Kernel white, albuminous, enclosing a large dicotyledonous leaf.

Composition.—The chief constituent is (1) *Ricinolein*, a mixture of glycerides of *ricinoleic* and *isoricinoleic acids*. (2) *Ricinoleic acid*, a viscid oil, believed to be the purgative principle. (3) *Glycerides of stearic and dihydroxystearic acid.*

B.P. Dose.—60 to 240 ms. or 4 to 16 mils.

PHARMACOLOGY

Externally.—Like almond oil and olive oil, castor oil is bland and unirritating. Rubbed into the skin, or injected into a vein or the rectum, it purges. It increases the secretion of milk when applied to the breasts, but poultices of the leaves of the castor oil plant are more effective.

Internally. **Gastro-intestinal tract.**—Its local action on the stomach is the same as on the skin, unless it is rancid when it causes nausea, eructations and vomiting. It acts by the formation of alkali ricinoleate as a result of saponification in the duodenum, gently stimulates the intestinal glands and peristalsis, and is a painless, speedy, certain and fairly mild purgative operating within 2 to 6 hours. The stools are two to four in number, soft or semiliquid, but not watery, the oil being expelled with the last ones and occasionally causing griping. A portion of the oil is no doubt absorbed and when excreted by the mammary gland it may cause purgation to suckling babies. Some patients get habituated to its use, and in others it sets up after-constipation like rhubarb. X-ray examination after castor oil has shown that the colon becomes flaccid and does not recover its normal tone and mobility for two to three days. This possibly explains the cause of after-constipation.

THERAPEUTICS

Externally.—It may be used like olive or almond oil. A drop of castor oil let fall on the conjunctiva allays irritation caused by a foreign body. It is employed as a basis of many hair-oils and pomades.

Internally.—It is the safest and best **purgative** for children, the old and infirm, delicate females, women during and after pregnancy, and persons subject to piles and fissure of the anus. In abdominal operations, pelvic diseases, peritonitis, fevers, especially in the constipation of typhoid fever, castor oil is the safest purgative to be used. **Diarrhœa,** infantile or otherwise, caused by indigestible or undigested food, yields to a dose of castor oil with or without a minute dose of Tr. Opii. It is an excellent remedy for **acute dysentery,** when given with opium which prevents griping, at the very onset. (Castor oil 1 to 3 drs. and Tr. Opii 5 to 15 ms.). Similarly in small doses (15 to 30 ms. with 5 to 10 ms. of Tr.

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Opii emulsified) it is serviceable in the chronic variety. As an enema it has been given with success in impaction of the large intestine and rectum.

Dosage and mode of administration.—It has been observed that a minimum dose of 30 ms. and a maximum dose of 8 ozs. are required to open the bowels of an adult. As a rule it is rarely necessary to use more than 4 to 6 drs. for a single dose to an adult. Children can bear sometimes large doses. A small teaspoonful is not a large dose for a new-born babe. The disagreeable smell and greasy and sickening taste can be very well covered by emulsification with mucilage of acacia, or with yolk of eggs, or by giving in capsules. The oil must be warmed in cold weather, before administration. Taken floating on hot coffee, or half a teacup of warm water drunk two hours after a dose of the oil often helps its operation. Food retards or delays its action. A few drops of oil of turpentine mixed with the oil increases its purgative effect.

3. Anthracene Purgatives

The drugs of this group—aloe, rhubarb, senna and cascara—owe their properties to the presence of *anthracene* ($C_{14}H_{10}$) derivatives of anthraquinone. All contain *emodin* or trioxymethylanthraquinone; rhubarb and senna also contain *chrysophanic acid* or dioxymethylanthraquinone, which colours the urine yellowish-brown. They have an excellent action, being neither too mild nor too strong a purgative. The synthetic preparation, phenolphthalein, has a similar composition and is considered under this heading. All these are valuable in habitual constipation, especially that of atonic type, but are not so good in spastic constipation, and in the presence of acid fermentation in the intestine there may be no cathartic effect. As a rule they do not act so well, or may fail in the absence of bile, but they may be made active by the addition of soap or an alkali. Their main action is on the large intestine, consequently they take about 10 to 15 hours to produce their effect. Since they act by increasing the contraction of the intestinal muscles they often cause griping and they are largely combined with belladonna, hyoscyamus or some volatile oil.

ALOE

Aloes. *N.O. Liliaceæ*

Syn. I.V.—*Musabar*, Beng., Hind.

Source.—The liquid, evaporated to dryness, which drains from the leaves cut from various species of *Aloe*. Known in commerce as Cape, Curacao, Socotrine, or Zanzibar aloes.

Characters.—Dark-brown or greenish-brown glassy masses; transparent in thin fragments (Cape aloes); or dark chocolate brown,

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opaque masses with a dull, waxy, uniform fracture (Curacao aloes); or hard, dark-brown, opaque masses with an uneven porous fracture (Socotrine aloes); or dark reddish-brown, opaque masses with a nearly smooth and slightly porous fracture (Zanzibar aloes); odour, characteristic; taste, nauseous, bitter. *Solubility.*—Almost entirely in alcohol (60 p.c.).

Composition.—(1) A crystalline glycoside *Aloin* (Barbaloin). (2) *Aloe-emodin*, or trioxymethylanthraquinone. (3) *Resin*. (4) *Volatile oil, gallic acid*, a trace.

B. P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

Enters into.—Pil. Rhei Co., Pil. Colocynth. et Hyoscyam., Tr. Benzoin. Co., and the

Official Preparations

1. **Pilula Aloes.—B.P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.**
2. **Pilula Aloes et Ferri.**—About $\frac{1}{5}$ gr. iron sulphate in each 8 gr. pill. **B.P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.**
3. **Pilula Aloes et Asafœtidæ.**—$2\frac{1}{2}$ gr. aloe in each 8 gr. pill. **B.P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.**

ALOINUM

Aloin

Source.—A mixture of crystalline principles obtained from aloes.

Characters.—A pale yellow microcrystalline powder; inodorous; taste, bitter. *Solubility.*—Almost entirely in water, in alcohol (90 p.c.).

Composition.—*Barbaloin* and *isobarbaloin* in equal proportions. Barbaloin is a *methyl-anthraquinone* derivative of a glycosidal character.

B.P. Dose.—$\frac{1}{4}$ to 1 gr. or 0.015 to 0.6 grm.

Pharmacology

Externally.—The activity of aloes is due to aloin. On the unbroken skin it has no action, but is absorbed from a denuded surface which it stimulates. If sprinkled over an ulcer, it causes purging.

Internally. **Gastro-intestinal canal.**—In minute doses, aloes acts on the stomach as a **stomachic, bitter tonic**. Its action is not so marked on the small intestine, beyond slightly increasing the flow of bile, but it powerfully stimulates the muscular fibres of the colon, and slightly increases its glandular secretion. Therefore it is a **cathartic**, but its action is slow, taking 10 to 12 hours to purge. Large doses do not necessarily act earlier, but operate more violently and are accompanied by pain, griping, tenesmus and even bleeding from the rectum. In moderate doses the stools are soft, dark-coloured and formed and in large doses they are liquid. The slowness of its action is believed to be due to the fact that aloin cannot produce catharsis unless it is decomposed in the intestine into a more potent product by admixture with bile. Soap or alkalies combined with it help its solution, and to a certain extent prevent griping. The griping is caused by the irregular contractions of the colon. It

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increases the vascularity of the rectum, therefore the constant use of aloes may cause hæmorrhoids. When given as an enema it kills thread-worms. Aloin causes less griping.

Uterus.—Aloin injected into animals stimulates uterine muscle, and its administration by the mouth is followed by increased contraction. Moreover by stimulating the pelvic circulation it causes congestion of the uterus. It is therefore an emmenagogue and may act as an abortifacient when given to pregnant women.

Elimination.—Emodin is excreted in large quantities with the milk, for suckling babies are purged when it is given to their mothers. Aloes is also eliminated to a slight extent with the urine.

Therapeutics

Externally.—The Indian bazaar aloes (*musabar*) with turmeric or opium made into a paste is considered by the people of India as an effective remedy for contusions and swellings, but it remains to be proved how far it is beneficial in this respect.

Internally. **Gastro-intestinal tract.**—Aloes is reckoned as a valuable purgative in chronic and habitual constipation, for it does not cause after-constipation, and gains instead of losing its activity by repetition. It is ordinarily given in the form of a pill with rhubarb, nux vomica, ipecacuanha or colocynth. Its griping property is corrected by carminatives and extract of belladonna or hyoscyamus. An enema of aloes may be used as an anthelmintic.

Female diseases.—Aloes is given with success in amenorrhœa and delayed menstruation, especially when associated with dyspepsia and chronic constipation. When given with iron as Pilula Aloes et Ferri, it is very serviceable in anæmia, chlorosis and amenorrhœa of young girls.

Caution.—Aloes is contra-indicated in pregnancy; irritable conditions of the pelvic organs, especially rectum, hæmorrhoids, menorrhagia, and during the nursing period of mothers.

Prescribing hints.—Aloes is ordinarily given in the form of a pill. Aloin gr. 4, Strychnine Sulph. gr. $\frac{1}{4}$, Pulv. Ipecac. gr. 6, Ext. Belladonna gr. $1\frac{1}{2}$. M. Divide into 20 pills. One pill daily in habitual constipation after dinner. Extract of liquorice disguises its nauseous taste.

RHEUM

Rhubarb

Syn.—Rhei Rhizoma; Turkey Rhubarb.

Source.—Rhizome of *Rheum palmatum*, and other species of Rheum, cultivated in China and Tibet, deprived of most of its bark, and dried.

Characters.—In compact cylindrical, barrel-shaped, conical or

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planoconvex, or irregular pieces. The surface sometimes covered with a bright yellowish-brown powder. Rounded or angular, smooth, showing beneath dark red lines, intermixed with the reddish-brown substance of the root, usually presenting small scattered, star-like marks. Frequently the pieces are bored with a hole which sometimes contains the remains of the cord used to suspend them while drying. The root is hard and compact presenting a marbled, red and white appearance. Odour characteristic, aromatic. Taste, bitter, slightly astringent.

Composition.—(1) *Chrysarobin* is the chief, and is the colouring and purgative principle. (2) *Chrysophanic acid*, or dioxymethylanthraquinone, probably formed by the oxidation of chrysarobin. (3) *Emodin*, or trioxymethylanthraquinone. (4) *Rheo-tannic acid*. (5) Oxalate of lime. (6) Other substances, as rheumic acid, resin, starch, etc.

B.P. Dose.—3 or 15 grs. or 0.2 to 1 grm.

Official Preparations

1. **Pilula Rhei Composita.**—About 2 grs. rhubarb in 8 grs. **B.P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.**
2. **Pulvis Rhei Compositus.** *Syn.—Gregory's Powder.*—15 grs. in 60 grs. **B.P. Dose.—10 to 60 grs. or 0.6 to 4 grm.**
3. **Tinctura Rhei Composita.**—10 p.c. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Pharmacology

Externally.—The percentage of chrysarobin in rhubarb is not enough to produce any local action by direct application.

Internally. **Alimentary canal.**—Rhubarb tinges the saliva and increases its flow. In small doses (2 to 5 grs.), it stimulates the secretion of the gastric juice and the peristalsis of the stomach. It is therefore a **stomachic** and **tonic**. In the intestine, it performs two definite functions. (1) In large doses (20 to 30 grs.), it increases the secretion of the intestinal glands and the peristaltic movements, and thus acts as a mild **purgative**. This is the result of the effects of chrysophanic acid and emodin, both anthraquinone derivatives. Purging occurs within 4 to 8 hours often accompanied by griping, and the stool is liquid and yellow, the colour being derived from the excess of bile and chrysarobin, the pigment. (2) After opening the bowels, the rheo-tannic acid constipates by arresting the glandular secretion of the intestine. This **astringent** action may also be produced by small doses of the drug, but the action of rheo-tannic acid is slower than that of chrysarobin.

Elimination.—Chrysarobin has been found in the milk, and largely in the urine, both of which are coloured by it. Large doses may even lead to irritation of the kidney. It makes the milk bitter and purgative. Rheo-tannic acid is excreted by the bowels.

Therapeutics

Internally.—Rhubarb is largely employed as a stomachic and laxative in infantile ailments. It is an excellent remedy

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for the dyspepsia of children, especially when caused by a faulty diet. It expels undigested food, and produces first a soothing and afterwards an astringent effect. Goodeve's Red Mixture (*see* p. 100) is largely employed for this purpose in this country. In fact, it is one of our every day nursery remedies. Similarly, it is most effective in controlling infantile diarrhœa, produced by undigested food, or other irritating matter; here we look for the after astringent effect. Gregory's powder, which may be administered with milk, is a very useful aperient in many gastric and abdominal troubles of children. As a pure purgative it cannot be prescribed alone, on account of its griping and after-constipating properties, but combined with an equal quantity of soda, or with other purgatives, as Pil. Rhei Co., it may be given for this purpose. A full dose of Gregory's powder often cuts short an attack of mucous diarrhœa or dysentery, if given at the onset.

SENNAE FOLIUM

Senna Leaf

Source.—Consists of dried leaflets of *Cassia acutifolia* (Alexandrian senna), and of *Cassia angustifolia* (Tinnevelly senna).

Characters.—Pale greyish-green or yellowish-green, thin brittle; 20 to 50 mm. long and 5 to 16 mm. wide; lanceolate or ovate-lanceolate; unequal at the base with entire acute lamina; distinct veins on the under surface; scattered hairs on both surface. Odour, slight; taste, mucilaginous, slightly bitter, and characteristic.

Composition.—The composition is not well known. Contains four glycosides (1) *rhein*, (2) *aloe-emodin*, (3) *kæmpferol*, and (4) *isorhamnetin*, (5) Anthraglucosennin, a mixture of several substances, (6) Cathartic acid.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm.

Official Preparations

1. **Confectio Sennæ.**—10 p.c. **B. P. Dose.—60 to 120 grs. or 4 to 8 grm.**
2. **Pulvis Glycyrrhizæ Compositus.**—Senna 16 p.c. **B.P. Dose.—60 to 120 grs. or 4 to 8 grm.**

SENNAE FRUCTUS

Senna Fruit

Syn.—Senna Pod.

Source.—The dried ripe fruits of *Cassia acutifolia* (Alexandrian senna pods), and of *Cassia angustifolia* (Tinnevelly senna pods).

Characters.—Alexandrian fruit, pale green with a brown central area; flat and thin, broadly oblong or somewhat reniform; 4 to 6 cm. long and up to 2.5 cm. wide; rounded at the apex, base sometimes ending in a short stalk. Pericarp, dry membranous, with about 6 seeds, flattened, obovate-cuneate seeds. Odour and taste, slight.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm. (4 to 12 pods).

Official Preparations

1. **Extractum Sennæ Liquidum.—B.P. Dose.—10 to 30 ms. or 0.6 to 2 mils.**

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2. Syrupus Sennæ.—25 p.c. B.P. Dose.—30 to 120 ms. or 2 to 8 mils.

3. Infusum Sennæ Concentratum.—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.

4. Infusum Sennæ Recens.—B.P. Dose.—½ to 2 oz. or 15 to 60 mils.

5. Mistura Sennæ Composita. *Syn.—Black Draught.*—B.P. Dose.—1 to 2 oz. or 30 to 60 mils.

Pharmacology

Senna is a **laxative** or brisk **purgative** according to the dose used. The anthraquinone derivatives stimulate both the secretion and peristaltic action of the intestines, almost entirely the large intestine, and produce pale yellow watery stools containing some undigested food. It is not a cholagogue. Large doses cause griping. It possesses none of the tonic effects of rhubarb ; on the other hand, purgation by senna does not cause subsequent constipation. It may however cause the urine to be red. Injected into the viens, it causes vomiting and purging. It is eliminated with all the secretions and will purge the child when given to nursing women.

Therapeutics

Senna is a safe purgative in slight cases of simple constipation and fæcal accumulation, but, on account of its tendency to gripe and nauseous taste, it is rarely given alone.

It is largely used *to complete the effect of duodenal purgatives* in the form of a blue pill at bedtime and black draught in the morning. The compound liquorice powder is to be preferred to the black draught, as it is a very nasty mixture. This preparation is largely used in habitual constipation and the constipation of pregnancy. Confection of senna, either with or without sulphur, is a valuable laxative in hæmorrhoidal conditions.

Prescribing hints.—The griping property of the black draught may be prevented by adding a few minims of tincture hyoscyamus. In the form of compound liquorice powder senna is largely used as a safe mild purgative. Infusion of senna pods is more active and causes less griping, and is very useful in cases of habitual constipation. Six to eight pods form the usual dose.

CASCARA SAGRADA

Cascara Sagrada

Syn.—Rhamni Purshiani Cortex ; Sacred Bark.

Source.—The dried bark of *Rhamnus Purshiana* (California buckthorn).

Characters.—In quilled, channelled, or nearly flat pieces. 1 to 2 mm. thick, 10 to 20 cm. in length. Cork smooth, purplish-brown,

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almost covered with patches of silvery-grey lichens. Inner surface reddish-brown, longitudinally striated. Odour characteristic. Taste, nauseous, bitter and persistent.

Composition.—(1) *Emodin*, and (2) an allied substance possibly identical with *Frangula-emodin*. It also contains fat (2 p.c.), glucose, etc., *volatile oil*. Chrysarobin or chrysophanic acid is not present.

B.P. Dose.—20 to 60 grs. or 1·2 to 4 grm.

Official Preparations

1. **Extractum Cascaræ Sagradæ Siccum.—B.P. Dose.—2 to 8 grs. or 0·12 to 0·5 grm.**
2. **Extractum Cascaræ Sagradæ Liquidum.—B.P. Dose.— 30 to 60 ms. or 2 to 4 mils.**
3. **Elixir Cascaræ Sagradæ.—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Pharmacology

In small doses (5 to 10 ms.) of the liquid extract, cascara has a decidedly tonic effect on the stomach, promoting appetite and helping digestion. In moderate doses (½ to 1 dr.) it gently stimulates glandular secretion, but its action is upon the peristaltic movements of the bowels. Hence it is a laxative, producing healthy, copious and bilious stools. In large doses it is a gastro-intestinal irritant.

Therapeutics

Cascara is the most valuable aperient we have for habitual constipation, due to torpidity either of the liver or of the intestines. The dose ought to be so regulated as to produce a soft, painless, natural motion every morning, and when the desired end is gained, it should then be gradually reduced. The great advantage of the drug is that the dose does not require to be increased to maintain its action. However, for the successful cure of constipation it must be continued for at least 2 or 3 months.

Prescribing hints.—The solid extract is best given in pills either alone or with nux vomica and aloes. The nauseous taste of the liquid extract may be concealed by aromatics and glycerin or aromatics and chloroform. The plain aromatic syrup is not an unpleasant vehicle. The elixir is a pleasant preparation. The uncertainty of its action is sometimes most annoying to the physician. This chiefly arises from the use by the manufacturers of inferior bark or the barks of allied species.

PHENOLPHTHALEINUM

Phenolphthalein. $C_{20}H_{14}O_4$

Syn.—Purgen.

Source.—Obtained by heating phenol with phthalic anhydride and sulphuric acid, and purifying the product.

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Characters.—A white, or yellowish-white, crystalline or amorphous powder, soluble in alcohol (90 p.c.), almost insoluble in water. No odour, no taste.

B.P. Dose.—1 to 5 grs. or 0·06 to 0·3 grm.

Non-official Preparation

1. **Tab. Phenolphthaleini Co. B.P.C.**—Each contains phenolphthalein 1 gr., ext. belladonna sic. 1/100 gr., strychnine sulphate 1/500 gr. In habitual constipation. *Dose.*—1 to 5.

Action and Uses

Phenolphthalein in neutral solution is absolutely colourless, but on the faintest trace of alkali it turns delicate pink, Clinically it is used as an indicator in combination with decinormal soda solution, in the process of estimating the total acidity of gastric contents. Under the name of "*Purgen*" it has been introduced as a purgative, being specially useful in cases where prompt action is required. It is dissolved by the bile or alkali and produces a mild irritant action in the small intestine, but powerfully irritates the colon, producing loose motions without any griping in from 6 to 12 hours. For ordinary patients ½ to 3 grs. is a sufficient dose, but patients confined to bed may require as much as 10 grs. Part of the drug is absorbed and re-excreted in the bile and thus keeps up its action for several days. It has no action on the kidneys, but a small amount is excreted in the urine which it colours pink if alkaline. It is very safe and efficient in its action, but its use is contra-indicated in cases where there is a tendency to piles. It sometimes causes a rash in susceptible persons. Tetra-chlor-phenolphthalein given hypodermically (0·4 grm. in neutral olive oil 20 c.c.) is excreted by the bile and re-absorbed from the intestine and acts as a purgative.

The bromine and iodine compounds of phenolphthalein (Bromo-ray and Iodo-ray) are moderately opaque to X-ray and are used to take photographs of the gall-bladder.

4. Drastic Purgatives

IPOMOEA

Ipomœa

Syn.—Mexican Scammony Root. Orizaba Jalap Root.

Source.—Dried root of *Ipomœa orizabensis.*

Characters.—In irregular, tough or fibrous pieces, of varying size and shape; often in portions, 3 to 5 cm. wide and 2 to 4 cm. thick, which are transverse slices of large roots. Externally greyish-black and wrinkled, internally greyish or brownish. Slight odour; taste, faintly acrid.

B.P. Dose.—5 to 20 grs. or 0·3 to 1·2 grm.

SCAMMONIAE RESINA

Scammony Resin

Syn.—Resin of Ipomœa.

Source.—A mixture of resins obtained from Ipomœa.

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Characters.—Brownish, translucent pieces, brittle. Fracture resinous. Odour, characteristic, fragrant. Does not form an emulsion with water. Soluble in alcohol and ether.

B.P. Dose.—½ to 3 grs. or 0·03 to 0·2 grm.

Pharmacology

Scammony or scammony resin acts like jalap. Its action begins only when it mixes with the bile in the duodenum. It is the taurocholate and glycocholate of soda of the bile that help its activity. It powerfully stimulates (*a*) the secretion of the intestinal glands, and (*b*) the muscular coat, though the contraction is irregular. As a result, free purgation occurs with griping in about four hours; the stool is first soft, but soon becomes thin and watery. It is therefore a smart hydragogue purgative. It does not purge when injected into the blood, hence its action is entirely a local one. In large doses it causes gastro-enteritis. It is used to complete the effect of vermifuges for round and tape-worms.

Therapeutics

Internally.—Scammony or scammony resin is rarely used alone on account of its griping qualities. By combining it with other purgatives, its own severity of action is mitigated, while the action of others is promoted. It acts promptly when given with an alkali; soap answering well. In severe constipation or impaction of fæces the powder can be given with advantage, care being taken that there is no gastro-intestinal irritation.

On account of its hydragogue properties it can be given in cases where depletion is necessary, as in apoplexy or cerebral congestion or where some effused fluid is to be absorbed, as in dropsy. Jalap answers better in such cases.

It can be used for the expulsion of intestinal worms after a dose of santonin.

JALAPA

Jalap

Source.—The dried tubercles of *Ipomœa purga.*

Characters.—Dark brown; oblong, napiform or fusiform; 3 to 15 cm. or more long; larger ones incised; hard, compact, and heavy. Externally furrowed, wrinkled with small transverse scars. Internally yellowish-grey to dingy brown. Transverse section shows irregular, dark concentric lines. Odour, characteristic. Taste, sweet at first, acrid and disagreeable afterwards.

Composition.—(1) *Resin* 9 to 18 p.c., it appears to be identical with the resin obtained from scammony root. (2) *Jalapin* 10 p.c. insoluble in ether, also termed *Convolvulin* and *Jalapurgin.*

Official Preparations

1. **Jalapa Pulverata.** *Syn.—Pulvis Jalapæ.*—Jalap reduced to a fine powder, adjusted, if necessary, with suitable quantity of exhausted powdered jalap, or powdered lactose. Contains not less than 10 p.c. of resin. **B.P. Dose.—5 to 20 grs. or 0.3 to 1.2 grm.**

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2. **Pulvis Jalapæ Compositus.**—30 p.c. **B.P. Dose.**—10 to 60 grs. or 0.6 to 4 grm.

Pharmacology

Jalap closely resembles scammony in action with this difference, that (1) it is less irritant and contracts less violently the intestinal muscular fibres, and therefore causes less griping; and (2) it produces a greater stimulation of the intestinal glands, and is therefore more hydragogue. It does not purge unless in contact with the bile. *Small doses* have a laxative effect, but large ones produce several watery stools attended with pain and griping. Its action is entirely local, for it does not purge when subcutaneously injected.

Therapeutics

Being a hydragogue purgative, Pulv. Jalap. Co. is employed in drawing off water in dropsy, ascites, and anasarca from whatever cause they may arise. It is also used in obstinate constipation, and is a revulsant in congestion of the brain, apoplexy, and engorgement of the right heart. Jalap is an excellent purgative in Bright's disease and uræmia. The resin in small doses can be given in habitual constipation. It should not be prescribed where the bowels are inflamed or liable to inflammation.

OLEUM CROTONIS

Croton Oil. (*Not official*)

Syn.—Oleum Tiglii.

Syn. I. V.—*Jaipaler tel*, Beng., *Jamalgota ka tel*, Hind.

Source.—The oil expressed from the seeds of *Croton Tiglium*.

Characters.—Brownish-yellow to dark reddish-brown; viscid; odour, disagreeable. Taste, acrid, burning.

Identification of seeds.—The seeds are oval or oblong, dark brown, marked with ramification of the raphe. They resemble castor-oil seeds, which are brighter, polished and mottled.

Composition.—(1) *Croton* resin, a powerfully vesicant substance, appears to be the active principle. (2) Glycerides of stearic, palmitic, lauric, valeric, oleic, linolic and tiglic acids.

Dose.—½ to 1 m. or 0.03 to 0.06 mil.

Action and Uses

It is a powerful irritant to the skin. When taken internally undiluted it irritates the mouth and fauces, followed by griping and abdominal pain and within an hour or two by repeated purging. It is a drastic purgative. It is used only when the patient is unconscious as in *cerebral hæmorrhage*, *coma*, and in insanity on account of the minute dose and rapid and complete evacuation of bowels which follows. It is best given in pills, or mixed with butter or honey and placed at the back of the tongue.

COLOCYNTHIS

Colocynth

Syn.—Colocynthidis Pulpa; Bitter Apple. **Syn. I.V.**—*Makhal phal*, Beng. *Indrabaruni*, Sans.

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Source.—The dried pulp of the fruit of *Citrullus Colocynthis*. Contains not more than 5 p.c. of the seeds and 2 p.c. of outer sclerenchymatous part of the pericarp.

Characters.—White, spongy, light fragments. The powdered pulp exhibits abundant debris of large, thin-walled parenchymatous cells but no starch. No odour. Taste, bitter.

Composition.—(1) *Colocynthin*, a bitter amorphous purgative resin. (2) An amorphous purgative alkaloid. (3) *Mucilage* and *gummy matter*.

B.P. Dose.—2 to 5 grs. or 0.12 to 0·3 grm.

Official Preparations

1. **Extractum Colocynthidis Compositum.—B.P. Dose.—2 to 8 grs. or 0.12 to 0.5 grm.**
2. **Pilula Colocynthidis et Hyoscyami.—12.5 p.c. B.P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.**

Pharmacology

Internally.—In minute doses colocynth is a bitter tonic. In moderate doses it stimulates the intestinal glands and the muscles causing watery evacuations and griping. Hence it is a hydragogue drastic purgative. These effects may be produced if the drug is given either by the mouth or hypodermically, or injected into the circulation. In large doses these actions are aggravated and there is an intense gastro-intestinal irritation, reflexly affecting other abdominal and pelvic organs. It may therefore cause abortion.

Therapeutics

Internally.—It is rarely prescribed for its tonic virtue, but is often given in combination with aloes and mercury in constipation due to hepatic disorder. It is an excellent purgative to relieve portal engorgement. It should always be given with hyoscyamus or belladonna to prevent griping. Hence pil. colocynth. et hyoscyami is a valuable preparation. Because of the watery character of the stools, it may sometimes be given in **ascites, dropsy** or **cerebral congestion,** but scammony and jalap are more powerful in this respect.

Caution.—It should not be given either to pregnant women or to persons who are subject to diarrhœa, dysentery, piles or gastro-intestinal congestion.

5. Cholagogue Purgatives

PODOPHYLLUM

Podophyllum

Syn.—Podophyllum Root; Podophylli Rhizoma.

Source.—The dried rhizome and root of *Podophyllum peltatum*, American May Apple or Mandrake.

Characters.—Nearly sub-cylindrical, about 5 mm. thick; externally dark reddish-brown, smooth, or slightly wrinkled cylindrical pieces; presenting at intervals enlargements, which are marked on the upper

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surface by a depressed circular scar, and on the under surface stout, brittle rootlets, or their scars. Fracture short. Internally white, starchlike, or pale yellowish-brown and horny. Odour, characteristic Taste, bitter, acrid.

Composition.—It is composed of (1) a neutral cystalline substance, *Podophyllotoxin* (0.2 to 1 p.c.), and (2) *Podophylloresin*, an amorphous resin, both of which are purgative. (3) *Picropodophyllin*, quercetin and starch.

B.P. Dose.—2 to 10 grs. or 0.12 to 0.6 grm.

PODOPHYLLUM INDICUM

Indian Podophyllum

Syn.—Podophylli Indici Rhizoma.

Source.—The dried rhizome and roots of *Podophyllum emodi.*

Characters.—Irregular and tortuous ; knotty, 2 to 4 cm. long, and 1 to 2 cm. thick, flattened dorsiventrally. 3 to 4 cup-shaped scars on the upper surface ; numerous root scars or stout roots on the under surface. Yellowish-brown to earthy-brown externally, fracture, short, internally pale brown and starchy and horny surface. Odour, slight, characteristic ; taste, somewhat bitter and acrid.

B.P. Dose.—2 to 10 grs. or 0.12 to 0·6 grm.

Official Preparation

1. **Podophylli Resina.** *Syn.—Podophyllin ; Vegetable Calomel.*—A mixture of resins obtained from Podophyllum, or from Indian Podophyllum. Pale yellow to yellowish brown amorphous powder, or brownish-grey masses ; turns darker on exposure to light or heat. Characteristic odour, with bitter, acrid taste. **B.P. Dose.—$\frac{1}{4}$ to 1 gr. or 0.015 to 0.06 grm.**

Pharmacology

Externally.—The resin acts as an irritant to the unbroken skin. The dust coming in contact with the eyes causes conjunctivitis. It is absorbed from raw surfaces and produces its specific effects, *i.e.*, purgation.

Internally. **Gastro-intestinal tract.**—Being bitter and acrid in taste, podophyllin may excite salivation. It is a powerful hydragogue purgative. In purgative doses it causes griping, perhaps nausea, and within 10 to 12 hours a free watery stool. Much of the force of the drug is directed to the small intestine, more specially the duodenum, whose contents it sweeps along rapidly, in which respect it resembles calomel. Hence it has received the name of "vegetable calomel." Beyond this it has none of the other properties of calomel. Impure resin produces more griping and common salt increases its cathartic effect. In large doses it gives rise to gastro-intestinal irritation. Bile dissolves the drug. As a purgative its action varies with different individuals, some being more susceptible than others.

Liver.—Probably the greater amount of bile found in the fæces after the use of this drug is due, not so much to increased

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secretion, as to diminished absorption owing to more rapid peristalsis not giving time for such absorption.

Absorption.—It is absorbed by raw surfaces, mucous and serous membranes and cellular tissue. It produces its specific effects even when injected into the veins.

THERAPEUTICS

Internally.—As a purgative it is an excellent remedy for constipation, due to hepatic disorder or otherwise; the griping being corrected by hyoscyamus, belladonna, or cannabis indica. Its action becomes more uniform and certain when combined with other purgatives, *e.g.*, aloes, jalap, colocynth, rhubarb. Calomel and podophyllin make a very advantageous combination, as they aid each other's action on the same portion of the intestine. Being an indirect cholagogue it is best suited for constipation caused by the torpid condition of the liver, biliousness or hepatic dyspepsia. $\frac{1}{6}$ to $\frac{1}{4}$ gr. can be recommended as an ordinary dose for habitual constipation, but $\frac{1}{4}$ to $\frac{1}{2}$ gr. should be given in obstinate constipation or to relieve **portal congestion.** Sometimes larger doses are necessary. Whey, sherbet or mucilaginous drinks stop excessive purging.

It is given in non-purgative doses ($\frac{1}{30}$ to $\frac{1}{20}$ gr.) in many functional disorders of the liver, characterised by metallic taste in the mouth, dull depressed spirits, sluggish bowels, sick headache, etc.

Prescribing hints.—One of the best ways of giving podophyllum is to dissolve it in Sp. Ammon. Aromat. (1 gr. to 1 dr.) as the resin then remains in solution on the addition of water.

Pill for habitual constipation and torpid liver.—Podophyll. Res. $\frac{1}{6}$ gr., Pulv. Ipecac. $\frac{1}{6}$ gr., Ext. Euonym. Sic. 1 gr., Ext. Nucis Vom. Sic. $\frac{1}{6}$ gr., Ext. Hyoscyami Sic. $\frac{1}{2}$ gr., Pil. Rhei Co. 2 grs. M. ft. Pil. mitte tales xii. Twice daily after breakfast and dinner.

IRIDIN

(*Not official*)

Syn.—Extractum Iridis, B.P.C.

Source.—An extract obtained from the root of *Iris versicolor*, the Blue Flag. A dark brown resinous powder, having a bitter acrid taste.

Dose.—1 to 3 grs. or 0.06 to 0.2 grm.

PHARMACOLOGY AND THERAPEUTICS

Iridin is used in biliousness and all sluggish conditions of the liver. It should be administered in the form of a pill made up with glycerin of tragacanth or extract of hyoscyamus. It may be usefully combined with euonymin and podophyllin.

EUONYMI CORTEX

Euonymus Bark. (*Not official*)

Source.—The dried root-bark of *Euonymus atropurpureus*,

Composition.—(1) A bitter crystalline alcohol *euonymol*, (2) the sterols, euonysterol, atropurpurol, and a mixture of fatty acids.

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Non-official Preparations

1. **Extractum Euonymi.** *Syn.—Euonymin.—Dose.*—1 to 2 grs. or 0.06 to 0.12 grm.
2. **Tr. Euonymi, B.P.C.**—Bark 4, Alcohol (45 p.c.) *q.s.* to 20. *Dose.*—10 to 40 ms. or 0.6 to 2.6 mil.
3. **Liquor Euonymini et Iridini, B.P.C.**—Ext. euonymus 320 grs., ext. iridis 160 grs., pot. carbonas 120 grs., water 5 oz., alcohol (45 p.c.) *q.s.* to 20 oz. *Dose.*—30 to 60 ms. or 2 to 4 mils.

Pharmacology and Therapeutics

The action of euonymin resembles in many respects that of podophyllin, but is milder. On the heart it has properties similar to digitalis. It is a very useful remedy in **hepatic disorders**, and in **constipation**, especially when it is due to torpidity of the liver. Combined with cascara, it may be given with very good results in chronic or habitual constipation. The following powder is very useful in infantile hepatic enlargement with slow fever:—Ext. Euonymi, $\frac{1}{2}$ gr., Pulvis, Ipecac. $\frac{1}{6}$ gr., Pulv. Rhei 2 grs., Salicinum 1 gr., Sod. Bicarb. 2 grs. M. ft. Pulv. Mitte tales 24. Twice or thrice daily.

GROUP X

DRUGS ACTING ON THE LIVER

The liver is by far the largest gland in the body and plays an important part in the general metabolism. Any derangement of its functions upsets the whole metabolic balance and produces diverse symptoms. It performs the following important functions:—(1) Formation of bile, which is partly secretory and partly excretory. It forms the bile pigment from the hæmoglobin which is excretory, and any disturbance of its function is characterised by jaundice, due to failure of the organ to excrete bilirubin. These pigments take no part in the digestive process but get mixed with the food in its passage through the intestine where they are broken up by the bacterial activity. The bile acids are secretory and help in the absorption of fats. These acids, or their products of decomposition, are partly absorbed from the intestine and are re-excreted by the liver. In the liver they stimulate the secretory cells and act as *natural cholagogues*. (2) Plays an important part in iron metabolism by conserving organic iron and forming hæmoglobin. It produces the anti-anæmic factor by the interaction between the intrinsic factor in the gastric juice and the extrinsic factor in protein food which is essential for the development of megaloblasts into normoblasts and reticulocytes in the bone-marrow. It is also supposed to help normal coagulation of the blood by forming fibrinogen. (3) Regulation of carbohydrate metabolism. By removing the excess of sugar from the portal blood and storing the excess as glycogen it maintains the concentration of sugar in the blood at a constant level of 0.12 p.c. In this function it is helped by the hormones of the pancreas, the adrenal medulla, the thyroid, and the pituitary gland. (4) Regula-

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tion of protein metabolism. It helps to metabolise amino-acids which are absorbed from the intestine as the end products of protein digestion. The ammonia salts formed as the result of protein digestion are converted into harmless urea. (5) Protects the body from the action of toxins either produced during metabolism or absorbed from the intestine. They are either excreted unchanged in the bile, or may be broken down or synthetised into harmless compounds, or may be stored in the organ to be excreted slowly. Many drugs and toxic substances are excreted by the bile. Sodium tetraiodophenolphthalein (*q.v.*) when given intravenously or administered *per os* is excreted into the gall-bladder rendering it opaque to X-ray. (6) Regulation of uric acid metabolism. This is not of much value in man.

Drugs that influence the secretion of bile.—Drugs that increase the secretion of bile are known as **cholagogues.** They may be direct and indirect. Bile is being continually secreted by the liver, and the gall-bladder acts as a storage reservoir, and ejects it intermittently into the intestine during digestion. Normally the entrance of the chyme into the duodenum is followed by contraction of the gall-bladder and this has been attributed to a hormone *cholecystokinin* formed in the duodenum by the entrance of acid chyme from the stomach. If the meal contains an excess of fat and protein or their products of digestion, the contraction is more powerful. The formation of secretin has also a stimulating effect both on the contraction of the gall-bladder and on the formation of bile. It does not mean that simply because more bile appears in the stool there is an increased secretion of bile; either the gall-bladder or the ducts have emptied more thoroughly, or the bile poured into the duodenum has been swept down without giving time for reabsorption.

Direct Cholagogues.—By far the best cholagogues are bile and bile salts, then come the salicylates and benzoates, soap and dilute hydrochloric acid. Mellanby has shown that secretin entering the blood stream excites the pancreatic secretion and bile, and any substance that helps the formation of secretin will increase secretion of bile.

Indirect Cholagogues.—These cause the bile to be rapidly swept along the intestine without allowing time for its reabsorption. The following drugs have a reputation of being indirect cholagogues. They are podophyllum, euonymus, iridin, ipecacuanha, mercuric chloride, colchicum, rhubarb, ammonium chloride, etc.

Drugs used to dissolve gall-stones are called **biliary lithontriptics.**—Inflammation of the gall-bladder or cholecystitis is a common affection and is often due to some bacterial infection. The chief organisms responsible are *B. coli, streptococcus,* and *B. typhosus or B. paratyphosus.* It

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may also result as an extension of inflammation from the duodenum. This is often associated with gall-stones. Several drugs have been used in cholecystitis, the most commonly used drug is hexamine (*q.v.*). In some cases specific vaccine gives good result. The treatment of gall-stones by drugs is very unsatisfactory. The following are used to expel, reduce or dissolve the stones, viz. sodium salicylate and aspirin make the bile watery, olive oil, etc.

Glycogenic function of the liver is stimulated by adrenaline, pituitrin and thyroxine which cause glycosuria by converting glycogen into glucose. Antimony, arsenic, phosphorus and opium depress the function.

EXTRACTUM FELLIS BOVINI

Extract of Ox Bile

Syn.—Fel Bovinum Purificatum.

Source.—Obtained by evaporating fresh ox bile to one-fourth of its volume, shaking it with alcohol (90 p.c.), filtering and evaporating the residue to the consistence of a firm extract. Contains the bile salts and pigments, free from mucus.

Characters.—A dark yellowish-green, plastic substance; taste, bitter and disagreeable. *Soluble* in water, and in alcohol (90 p.c.).

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Pharmacology and Therapeutics

Internally.—Bile is bitter, but cannot replace vegetable bitters as a stomachic. Given by the mouth most of it is absorbed in the intestine and carried to the liver which excretes it again, a small quantity of the bile acids being eliminated with the urine. It is a valuable cholagogue, and increases the secretion of both the solids and the fluids of the bile. The bile acids irritate the mucous membrane of the colon and act in the absence of bile. Bile increases the lipolytic ferment of the pancreas and helps the absorption of fats, and is therefore used in those cases of dyspepsia and constipation in which the natural secretion of bile is very deficient. 20 to 30 grs. of bile extract dissolved in 1 or 2 ozs. of water may be given as a clyster in cases of impaction of fæces in the rectum, where there is no room for a larger enema. It is generally given in cachets or in solution, but it is best administered in the form of keratin-coated or salol-varnished pills, two hours after food.

GROUP XI

ASTRINGENTS

Astringents form a special group of drugs whose action is characterised by contraction or shrinkage of the tissues and diminished exudation or secretion. Their effects are

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antagonistic to purgatives. They include the *astringent metals, acid sulphuric dilute, adrenaline* and the *vegetable astringents.* Opium and chalk act as intestinal astringents by diminishing the secretions and peristalsis.

The *vegetable astringents* owe their property to the presence of tannin. They precipitate proteins and form a blue or black compound with iron preparations. They are milder in their effects than the astringent metals, and being practically harmless they are specially used in diseases of the alimentary canal. All astringents are *local hæmostatics, i.e.,* check bleeding by precipitating a hard coagulum which plugs the bleeding vessels. They have no action on the vessel walls. Since astringents are precipitated by proteins they are not much absorbed, nor do they exist in the blood and tissues in sufficient quantity to be of any use. They have therefore no remote astringent effect, and act only on the part to which they are applied.

Tannic acid or substances containing it form more or less insoluble compounds with many metals, alkaloids, glycosides, etc., and may therefore be used as their antidotes.

Vegetable astringents are:—
Tannic acid, Catechu, Rhatany, Hamamelis, Myrobalan (*q.v.*)

ACIDUM TANNICUM

Tannic Acid

Syn.—Tannin; Digallic Acid.

Source.—Obtained from the galls of various species of *Quercus,* by subjecting them to special fermentation and extracting them with water-saturated ether.

Characters.—Yellowish-white or light brownish, glistening scales, light masses, or an impalpable powder; odour, characteristic; taste, slightly astringent. *Soluble* in 1 part of water and alcohol (90 p.c.), freely in acetone, slowly in 1 part of glycerin. An aqueous solution forms precipitates in solutions of gelatin, albumen and some alkaloids.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Official Preparations

1. **Glycerinum Acidi Tannici.**—15 p.c. **B.P. Dose.—10 to 30 ms. or 0.6 to 2 mils.**
2. **Suppositorium Acidi Tannici.**—0.2 grm. or 3 grs. each.
3. **Trochiscus Acidi Tannici.**—0.03 grm. or ½ gr. in each.
4. **Unguentum Acidi Tannici.**—20 p.c.

Non-official Preparations

1. **Acidum Acetyltannicum, U.S.P.** *Syn.—Di-Acetyl-tannin; Tannigen*—A Product obtained by the acetylisation of tannic acid. A yellowish or greyish-white powder. Darkens on exposure to light. Slightly soluble in water and in alcohol. In *enteritis* and *infantile diarrhœa. Dose, U.S.P.*—0.6 grm. or 10 grs.

2. **Albumini Tannas, U.S.P.** *Syn.—Albutannin.*—A compound of albumin and tannic acid. A yellowish white, odourless powder. Almost insoluble in water. *Dose, U.S.P.*—2 grm. or 30 grs.

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3. **Tannoform.** *Syn.—Methyl Ditannin.*—A condensation product of tannic acid and formaldehyde, in reddish-white powder insoluble in water. As a dusting powder in *hyperhidrosis, bed-sores, soft chancres, eczema,* etc. Internally in *infantile diarrhœa. Dose.*—5 to 15 grs. or 0·3 to 1 G.

PHARMACOLOGY

Externally.—Tannic acid or substances containing it coagulate albumin, gelatin and mucus, but gallic acid does not. Tannic acid has no action on the unbroken skin, but applied to an exposed mucous membrane or a denuded surface it coagulates the mucus and the albuminous secretions, and forms a firm insoluble pretective covering over the part. The coagulated albumin or gelatin resists putrefaction. Absorbed into the tissues, it coagulates the interstitial fluids, and condenses the albuminous and connective tissues, and thereby diminishes the serous discharge. Hence it is a powerful local astringent. It arrests hæmorrhage partly by plugging the small vessels, and partly by the production of a coagulum in the surrounding tissues, but it has no action on the muscular coats. It is therefore a local hæmostatic. It slightly depresses the local sensory nerves, and has feeble antiseptic and irritant properties.

Internally. **Alimentary canal.**—Tannic acid causes dryness of the mouth with a feeling of astringency and of stiffness of the tongue and throat, owing to the coagulation of the secretions of the mucous membranes. These effects are due to the direct chemical effect on the protein. Its action on the stomach is the same as on the mouth. A portion of it is converted into tannate when it loses its astringent property till the tannate of albumin is redissolved in the gastric juice and tannin is again liberated. Pepsin and peptone are precipitated in a neutral solution, therefore they are not affected because of free acid, but large doses impair digestion by precipitating pepsin, and often cause gastric irritation and vomiting, but stop hæmorrhage by their local hæmostatic property. In the intestine it causes constipation by precipitating proteins and diminishing the glandular secretions, thus making the stools harder and drier. It precipitates yeasts and microbes and acts as a mild antiseptic and renders the fæces less offensive by decreasing the number of bacteria. The undecomposed tannates and unabsorbed gallates are thrown off with the fæces. Tannic acid cannot affect the biliary secretion.

Blood.—Tannic acid enters the blood mostly as gallates and partly as tannates and circulates as such. Injected into a vein it causes death by thrombosis.

Elimination.—There is a great diversity of opinion as to its excretion. According to some, any that has been absorbed is decomposed in the human body, only about 1 p.c. is detected in the urine or fæces; although gallates and traces

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of tannates are found in the urine of animals. But Stockman found gallic acid with traces of tannin in the urine when pure tannin was given by the mouth; and a large amount of tannin with a little gallic acid in the urine when sodium tannate was administered.

Therapeutics

Externally.—As a *local hæmostatic*, tannic acid is largely employed in hæmorrhages from the nose, the rectum, the bladder, the urethra, etc., although in these days, as a hæmostatic, it has been superseded by adrenaline. It may be used as a snuff or a nasal douche in epistaxis, or as an ointment or a suppository in hæmorrhoids. As a *local astringent*, it is useful in subduing mild forms of subacute or chronic inflammatory processes and discharge from the skin, as in eczema, intertrigo (Glycerinum Acidi Tannici); the ear in otorrhœa (Glycerinum Acidi Tannici); the eye, as in conjunctivitis and corneal vascularity (as collyrium 4 grs. to 1 oz.); the nose, as in ozæna (a douche, snuff or paint); the vagina, as in leucorrhœa (an injection, douche or pessary); the uterus, as in ulcerated os (pessary or cotton-wool soaked in tannic acid and glycerin); the bladder, as in cystitis (injection); and the rectum, as in ulcers, fissures and prolapse of the rectum (an injection or suppository.)

It is valuable in the treatment of **burns**, when applied as a dressing with 2½ p.c. freshly prepared solution and kept saturated till the area is tanned a mahogany brown. Recently it is used in 5 p.c. solution for children and 10 p.c. solution for adults. It diminishes pain, prevents fluid depletion, decreases toxæmia, and in the 2nd and 3rd degree of burns allows epithelisation to proceed while the membrane is in place. The great advantage of this treatment is the prevention of the absorption of toxin which generally causes death on the 2nd and 3rd day after the injury. When sprayed over the wound no dressing is applied and the spraying done every 15 minutes until a dry brown crust forms which seals the wound.

Internally. **Alimentary canal.**—Tannic acid makes a very good dentifrice for bleeding and ulcerated gums. Glycerin of tannic acid is a valuable application in ulcerative stomatitis, subacute or chronic sore-throat, relaxed or elongated uvula, enlarged tonsils, etc. A gargle (glyc. acidi tannici 1 dr. to 1 oz.), a spray (1 dr. in rose water 10 ozs.), or lozenges may be used in these cases. An insufflation of tannin with starch makes an excellent application for the mouth and larynx. It is a valuable remedy for gastric and intestinal hæmorrhage, but it should be given in large doses, say 30 to 40 grs. every one or two hours. It is a valuable antidote in poisoning by alkaloids and antimonial salts. It is largely

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used in diarrhœa either acute or chronic, but preparations of catechu are generally preferred.

Prescribing hints.—Internally it may be given in solution, cachets, or pills. In the absence of tannic acid any vegetable infusion containing tannin, such as strong tea or decoction of oak bark, may be employed in alkaloidal poisoning. It should not be combined with ferric salts which it colours black; with mineral acids it precipitates tannin, and with alkalies it forms soluble tannates, but the solution changes colour becoming black. Caffeine is precipitated by tannic acid but is redissolved if the latter be in excess.

CATECHU

Catechu

Syn.—Pale Catechu: Gambir. **Syn. I.V.**—*Khayer*, Beng., *Kath*, Hind.

Source.—A dried aqueous extract of the leaves and young shoots of *Uncaria Gambier*.

Characters.—In cubes, sometimes agglutinated. Each side about 25 mm. Dark, reddish-brown externally, pale cinnamon-brown internally; porous friable. Taste, at first bitter and astringent, then sweetish. No odour. *Solubility.*—Entirely in boiling water.

Composition.—*Catechu-tannic acid*, 22 to 50 p.c. (2) *Catechin* 7 to 33 p.c. (3) *Quercetin*, catechu-red, *gambier-fluorescein*, wax, oil, etc.

Incompatibles.—Alkalies, metallic salts, gelatin.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Official Preparation

1. **Tinctura Catechu.**—1 in 5. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Pharmacology and Therapeutics

Internally.—Catechu is a non-irritating **astringent**, acting like tannic acid, which it contains. It is a valuable *local astringent* and may be used in the form of dentifrice, gargle, or lozenge for spongy gums, mercurial and ulcerative stomatitis and relaxed throat. Catechu is a very useful remedy for diarrhœa and in the early stages of cholera, being often prescribed with opium and chalk.

KRAMERIA

Krameria

Syn.—Rhatany Root; Krameriæ Radix.

Source.—The dried root of *Krameria triandra*, Peruvian Rhatany.

Characters.—Nearly cylindrical, slightly flexuous, reddish-brown, 15 mm. thick; cork scaly with polygonal cells and dark-brown walls. Fracture, shortly fibrous in the bark, splintery in the wood; bark, bright reddish-brown, about one-third of the radius of the root in thickness. Wood, pale reddish-brown, finely radiated in transverse section. Odourless. Taste of bark astringent, wood nearly tasteless.

Composition.—(1) *Rhatania-tannic acid*, 8.4 p.c. (2) Rhatania red, the colouring matter. (3) Rhatannin, neutral substance.

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Incompatibles.—Alkalies, lime water, iron, lead salts and gelatin.
B.P. Dose.—10 to 30 grs. or 0·6 to 2 grm.

Official Preparations

1. **Extractum Krameriæ Siccum.—B.P. Dose.—5 to 15 grs. or 0·3 to 1 grm.**
2. **Tinctura Krameriæ.—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**
3. **Trochiscus Krameriæ.** *Syn.—Krameria Lozenge.*—1 gr. or 0.06 grm. in each.
4. **Trochiscus Krameriæ et Cocainæ.** *Syn.—Krameria and Cocaine Lozenge.*—1 gr. or 0.06 grm. of extract and $\frac{1}{20}$ gr. or 0.003 grm. cocaine hydrochloride in each.

Pharmacology and Therapeutics

Internally.—Rhatany is a powerful **astringent**, because of the tannic acid it contains. The powdered root forms an important ingredient in many dentifrices and the tincture in mouth-washes. A teaspoonful of tincture in 1 oz. of water, or the infusion of the root, makes a good gargle in relaxed sore-throat, spongy and ulcerated gums and mercurial stomatitis. Krameria and cocaine lozenge is very efficacious in sore-throat.

HAMAMELIS

Hamamelis

Syn.—Hamamelidis Folia; Witch Hazel Leaves.
Source.—The fresh or dried leaves af *Hamamelis virginiana.*
Characters.—Broadly oval, 7 to 15 cm. long, upper surface dark green or brownish-green, pale below, apex obtuse; base oblique, cordate and shortly petiolate; margin, sinuate; veins, pinnate and prominent on the under surface, which is furnished with stellate hairs. Taste, astringent, slightly bitter. No odour.
Composition.—(1) *Tannic acid;* (2) *Gallic acid;* a bitter principle; and volatile oil.

Official Preparation

1. **Extractum Hamamelidis Liquidum.—1 in 1. B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Non-official Preparations

1. **Tinctura Hamamelidis, B.P.C.**—Hamamelis bark in coarse powder, 100 grm.; alcohol (45 p.c.) q.s. 100 mil. *Dose.*—½ to 1 dr. or 2 to 4 mils.
2. **Unguetum Hamamelidis, B.P.C.**—Liquid extract of hamamelis, 10 mil., wool fat 50 grm.; yellow soft paraffin 40 grm.

Pharmacology and Therapeutics

As a local astringent or hæmostatic it has been used in various ways and in various affections in place of tannic acid. It may be used as a gargle in sore-throat, bleeding from the gums, ulcerative stomatitis, or as an injection in gonorrhœa, vesical hæmorrhage, nasal catarrh, epistaxis, etc. Hamamelis is a most valuable remedy for internal and external piles.

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GROUP XII
ANTHELMINTICS

Anthelmintics are drugs which kill or expel intestinal worms. *Vermicides* are remedies which kill the worms, while *vermifuges* expel them without necessarily killing them. Active peristalsis tends to remove intestinal parasites with other intestinal contents. Thus drastic purgatives are sometimes used for the purpose of expelling the worms with partial benefit. Since the worms fix themselves with their hooks, suckers or serrated margins, they must be weakened or narcotised or killed before they can be effectively expelled.

An ideal anthelmintic is one whose value depends not only upon its poisonous effects upon the parasites in the intestinal canal, but also upon its harmlessness as regards the patient, *i.e.*, the drug should exert its influence on the worms without being absorbed, and since it is desired to attack the worm rather than the host, the dose must be as large as can be borne by the patient without producing any toxic effect. Safe doses of the vermicides do not kill the parasites, but only depress or narcotise them, and these would recover if left in the intestine. It is therefore customary to follow the use of the vermicide with a purgative. This also prevents any absorption of the drug and so diminishes the toxicity. Magnesium sulphate half an ounce in water is an all round good purgative. Calomel may also be used followed by magnesium. Since many of these anthelmintics are soluble in oil and may help absorption, purgative oils are better avoided. In large doses most anthelmintics act as gastro-intestinal irritants.

In cases of infection with tape-worm or hook-worm, the use of an anthelmintic is usually preceded by a fast so that the parasite will not be protected by the intestinal contents. This however has the disadvantage of weakening the patient and also helping absorption of the drug. In any case the fast should not be severe. In mass treatment it is a great disadvantage and its use is disappearing specially with weak and debilitated patients. After a light evening meal a dose of purgative is given and the anthelmintic is taken first thing in the following morning either in one dose, or in two or three divided doses given every hour, to be followed two hours after the last dose by another dose of the purgative. Santonin is best given at bedtime on account of its effects on the retina.

A number of drugs belonging to other groups, for instance, oil of turpentine, Beta-naphthol, thymol and chloroform also enjoy the reputation as anthelmintics.

Apart from the infection of the human gut with helminthes, many worms inhabit the tissues of the host. They are chiefly the different varieties of Bilharzia (*Schistosoma)* and Filaria,

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the former giving rise to the condition known as Bilharziasis and the latter Filariasis.

Antimony and *emetine* have been used in the treatment of bilharziasis with some benefit. Emetine has also been used in infestation with *Fasciola hepatica* (Liver fluke) and *Paragonimus* (Lung fluke).

Filariasis has been treated with *arsenic* and *antimony* but the results were disappointing.

Anthelmintics are classified as follows :—

Class A : Anthelmintics for Round-worm
Santonin, Carbon Tetrachloride, Oil of Chenopodium, Butea Seeds *(q.v.)*

Class B : Anthelmintics for Tape-worm
Male Fern, Pelletierine Tannate, Melon Pumpkin Seeds *(q.v.)*

Class C : Anthelmintics for Hook-worm
Thymol *(q.v.)*, **Beta-naphthol** *(q.v.)*, **Carbon Tetrachloride, Oil of Chenopodium, Tetrachlorethylene, Hexyl-resorcinol**

Class D : Anthelmintics for Thread-worm
Rectal injections of a **solution of Common Salt**, strong infusions of **Quassia** and **Calumba**, solutions of **Ferric Salts** and **Decoction of Aloes**, and **Carbon Tetrachloride** by mouth

Class A : Anthelmintics for Round-worm

SANTONINUM

Santonin. $C_{15}H_{18}O_3$

Source.—A crystalline principle obtained from santonica, the dried unexpanded flower-heads of *Artemisia cina*, and other species of *Artemisia*.

Characters.—Colourless, flat, rhombic prisms, feebly bitter, turning yellow by sunlight. *Solubility.*—Almost insoluble in water, soluble in 2½ parts of chloroform and in 50 parts of alcohol (90 p.c.).

B. P. Dose.—1 to 3 grs. or 0.06 to 0.2 grm. ¼ to ½ gr. for a child 1 year old ; 1 to 1½ grs. for a child 2 to 5 years.

Pharmacology

Internally. **Intestines.**—Santonin is a direct poison to round-worms, *Ascaris lumbricoides*, killing them in the intestine. Its action is less marked on thread-worms, *Oxyuris vermicularis*, and it has no effect whatever on tape-worms. Some assert that it does not kill but paralyses the worm. In fact many worms are passed out alive. It is a valuable anthelmintic for round-worms, although it does not kill them outside the body. It is partially dissolved in the stomach and passes into the intestine where it acts as an anthelmintic. This effect is possibly due to an unknown oxidation product formed in the intestine. Sometimes a portion may be absorbed and though this may not give rise to any toxic symptoms there is yellow vision (xanthopsia) and colouration of the urine. In vermicidal doses it does not cause purgation, but does so when given in large quantities.

Absorption.—It is oxidised in the tissues and is excreted in the urine and fæces in the form of oxysantonins. After

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a therapeutic dose the entire quantity is eliminated by the urine as a coloured substance although traces of santonin may be detected in the urine after large doses.

Nervous system.—It produces some curious effects here. Even in medicinal doses, within an hour or two after administration, objects first appear bluish, and then greenish or yellow, due perhaps to a certain disturbance of the retinal fibres, for though there is hyperæmia of the retina, yet the humours and other tissues of the eye are not stained. Taste and smell are sometimes affected.

Kidneys.—Santonin is chiefly excreted by the kidneys, and during its passage increases their secretion. Sometimes it may create dysuria or incontinence of urine in children. It colours acid urine greenish-yellow and *alkaline urine purplish-red*, referable probably to an unknown oxidation product formed in the system and excreted with the urine.

Toxic action.—In large doses it causes headache, vomiting, purging, loss of consciousness and speech, cold sweats, depression of the heart and respiration, intense saffron-coloured urine, tremor, convulsions and death. Sometimes a rash appears on the skin. Poisoning occurred in a child from 1½ grs. On the other hand, recovery has taken place after swallowing 1 oz. of the drug. These poisonous symptoms have probably been due to impurities.

Therapeutics

Internally.—Santonin is chiefly employed for killing round-worms. It should be given at night on an empty stomach, after a mild purge in the morning, followed by a purgative next morning. Calomel is the best purgative to use. To a child 1 to 3 years old 1 to 2 grs. of santonin may safely be given followed by a purgative next morning. The best method is to prescribe it with calomel and sugar, followed, if necessary, by a dose of Gregory's powder or a saline next morning. It should be taken for three alternate nights. To avoid any toxic effects, castor oil should not be used with it. Crude yellow santonin is regarded by some as a valuable remedy in sprue. But it appears that without special diet it has no influence in modifying the course of the disease and that it is in no way a specific remedy.

Class B: Anthelmintics for Tape-worm

FILIX MAS

Male Fern

Syn.—Aspidium.

Source.—The rhizome and leaf-bases of *Dryopteris Filix-mas*. Collected late in the autumn, divested of roots, leaves, dead portions, and carefully preserved.

Characters.—From 7 to 15 cm. or more long. Rhizome about 2 cm. in diameter: entirely covered with curved angular, dark-brown bases of the fronds, which bear numerous ramenta brown externally, green

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internally. Transverse section shows 8 pale yellow fibrovascular bundles. Odour, slight. Taste, first sweetish and astringent then bitter and nauseous.

Composition.—(1) *Filmarone*, an amorphous substance to which its properties are due, in solution it slowly decomposes into (2) *Filicic acid*, and (3) *Aspidinol*. (4) *Flavaspidic acid*, and (5) *Albaspidin*.

B. P. Dose.—60 to 180 grs. or 4 to 12 grm.

Official Preparation

1. **Extractum Filicis.** *Syn.—Liquid Extract of Male Fern ; Oleoresina Aspidii.*—Contains 25 p.c. w/w of Filicin. **B. P. Dose.—45 to 90 ms. or 3 to 6 mils.**

Pharmacology and Therapeutics

Internally.—Male fern is a safe and reliable anthelmintic for tapeworm (*Tœnia solium*, *T. Mediocanellata* and *Dibothriocephalus*), but being a local irritant it causes vomiting. It should be given in fairly large doses (1 to 2 drs.) to adults on an empty stomach preferably in two divided doses, after the bowels have been cleared by a purgative, and should be followed again by a brisk purgative. It also expels *Ankylostomum duodenale*. As a rule the drug is not absorbed and produces no untoward symptoms. In rare cases and when a large quantity is used it acts as a violent irritant to the alimentary tract, giving rise to vomiting, purging which contains blood, and in more severe cases convulsion, coma, dyspnœa and ultimately death from collapse. The purified filicic acid is highly poisonous to mammals, and when given by the mouth acts as a gastro-intestinal irritant. It is very soon absorbed and produces toxic symptoms.

Prescribing hints.—The liquid extract is best given in fresh milk or emulsified with fresh mucilage of acacia and flavoured with chloroform water. The patient should lie down after taking the draught, because it is liable to make him sick. It is best given in the morning on an empty stomach after a purge the previous day. It should be followed 1 to 2 hours later by a brisk purgative, either sulphate of magnesia or compound jalap powder. Castor oil should not be used either with or after it, as the absorption of the toxic principle is favoured by the presence of oil. The purgative must be a powerful one so as to weaken the head of the worm and loosen its hold upon the intestine. The head must be carefully looked for in the stools, and if it is not found, a second dose of the drug should be given two or three days later so as to expel it. But if more time is allowed the worm grows again and gets strong.

PELLETIERINAE TANNAS

Pelletierine Tannate

Source.—A mixture of the tannates of the alkaloids obtained from the bark of the root and stem of *Punica Granatum*.

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Characters.—A light yellow, amorphous powder. Odourless; taste, astringent. Slightly soluble in water, more in alcohol (90 p.c.).
Incompatibles.—Alkalies, lime water, metallic salts.
B. P. Dose.—2 to 8 grs. or 0·12 to 0·5 grm.

Pharmacology

It is a valuable anthelmintic for tape-worm. In large doses it causes vomiting and purging. Pelletierine sulphate being soon absorbed by the stomach cannot kill the parasite in the intestine, and in large doses it produces certain constitutional symptoms such as dimness of vision, giddiness, muscular weakness and twitchings, etc. These symptoms do not follow the use of the tannate.

Therapeutics

Pelletierine should be administered on an empty stomach or better still after a dose of castor oil, and a brisk purgative, such as compound jalap powder should follow its use. Only fresh salts are reliable as they deteriorate on keeping. The decoction of the fresh root-bark is also a valuable tæniafuge.

The rind of the fruit is a valuable remedy for diarrhœa and dysentery. It is often used with good results alone in diarrhœa, and with the rind of *mangosteen* fruit (*Garcinia mongostana*), and with *kurchi* bark (*Holarrhena antidysenterica*) in the form of decoction in dysentery.

Class C: Anthelmintics for Hook-worm

CARBONEI TETRACHLORIDUM

Carbon Tetrachloride

Source.—May be prepared by the action of chlorine on carbon disulphide.
Characters.—A clear, colourless, volatile liquid; odour characteristic; taste, burning. Not inflammable. In contact with flame decomposes, giving off an acrid odour. Almost *insoluble* in water; miscible with dehydrated alcohol and ether. Sp. gr. 1·603 to 1·606.
B. P. Dose.—30 to 60 ms. or 2 to 4 mils.

Action and Uses

Carbon tetrachloride has been used as a general anæsthetic, but owing to the presence of carbon disulphide as an impurity and the depressant action on the circulation it is twice as toxic as chloroform. It is used as a fire extinguisher, as a rubber and fat solvent, as an ingredient in certain types of paint, and for delousing of clothes. Its use has been revived by Maurice Hall as an anthelmintic for hook-worm and has been extensively used for the purpose. It is a direct poison to *necator*, but is less efficient in *ankylostoma* infections, not more than 30 to 40 p.c. of the latter being

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cured. *Oxyuris* is also expelled in large numbers. It has been used with success in T. saginata, and Barlow recently used it in Fasciolopsis (liver fluke) in China. It is certainly a very effective and safe remedy for hook-worm, the worms being expelled dead and flaccid.

It passses through the stomach unchanged and probably some absorption takes place in both the small and the large gut. Absorption may be hastened by alcohol and fatty food. The bulk of the drug absorbed is excreted by the lungs.

The usual dose is 2 to 3 c.c. (30 to 45 ms.) for adults preferably in divided doses in gelatin capsules, or dissolved in water; for children the dose is 2 ms. for each year up to 15 years. As a rule no preliminary purge or rest in bed is required and the patient can be given the anthelmintic and the purgative (sulphate of magnesia) in one dose. This is of great importance in mass treatment. Sometimes it is given in combination with oil of chenopodium. This has the advantage of giving both the remedies in smaller doses, and since their effects on the human host are different and independent they produce no harmful effect, on the contrary act as synergists. The best method is to give 3 c.c. of carbon tetrachloride and 1 c.c. of oil of chenopodium followed by a saline. When round-worms are also present, these should be treated first, and one or two weeks should elapse before carbon tetrachloride is given.

It is cheap and can be obtained in pure and stable form, and is more efficacious than most other remedies. Appearance of toxic symptoms is the only drawback and it is a powerful poison to the liver. In the mass treatment considerable number of deaths occurred in the labour forces in the tea districts. Although some of them are attributed to ingestion of alcohol either shortly before or after taking the drug, a few cases can only be explained as due to special idiosyncrasy to the drug which cannot be detected by previous examination of the patient.

Chief toxic effects are headache, nausea, vomiting, melæna, tremors, tetany, narcosis and convulsion. Cases of fatty degeneration of the liver, kidney and other parenchymatous organs have been observed in post mortem examination.

To avoid toxic symptoms the treatment should not be given to alcoholics, and no food or alcohol should be given shortly before or after treatment. The liability to liver trouble may be avoided by previous use of glucose, 1 oz. daily, for two days.

Contra-indications.—Cirrhosis and other diseases of the liver and patients suffering from calcium deficiency. Administration of calcium and parathyroid counteracts the toxic effects when calcium deficiency is suspected. Ammonium chloride also produces the same effect.

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OLEUM CHENOPODII

Oil of Chenopodium

Syn.—American Wormseed Oil.

Source.—Oil distilled with steam from the fresh flowering and fruiting plants, excluding roots, of *Chenopodium ambrosioides* var. *anthelminticum*. Contains not less than 65 p.c. w/w of ascaridole.

Characters.—A colourless, or pale yellow, liquid; odour, characteristic and pleasant; taste, bitter and burning.

B.P. Dose.—3 to 15 ms. or 0.2 to 1 mil.

Action and Uses

The oil has a sharp burning taste and causes nausea and sometimes vomiting with a feeling of warmth in the stomach. It is rapidly absorbed from the intestine, depresses the heart and respiration and causes a fall of blood-pressure.

It is one of the most efficient anthelmintics for ankylostomum duodenale and also for round-worm. It has the advantage over other anthelmintics of being certain in action, and is one of the safest remedies. The action is due to the presence of *ascaridole*, but the exact mode of action on the worm is not known.

The preparations obtainable in the market vary a great deal in the irritant properties on the gastro-intestinal tract. Ordinary doses do not kill the worms but they are only paralysed, and a purgative helps their expulsion. The preliminary purgative is not regarded as essential, but an after-purgative removes the drug from the gut, lessens the risk of toxic action and helps to clear out of the bowels accumulated fæcal matter and the decomposing worms. The usual purgative is either magnesium sulphate or castor oil. Oils do not increase but lessen toxicity.

It is best given in the morning, in doses of 0.5 c.c. each for three doses every hour, either on sugar or in capsules, the patient being kept on light evening meal. The treatment is repeated every three or five days, until the parasites disappear from the stool. The dose may be taken to be 1 m. per year up to 11 years. For healthy adults, 20 to 30 ms. It can also be given in syrup of glucose.

Poisoning is rare unless it is given in very large doses. The symptoms are nausea, vomiting, abdominal pain, ringing in the ears, deafness, and in fatal cases coma and convulsion, death taking place from respiratory failure. Different samples vary in their activity and some samples are very unpleasant to take.

If the dose is carefully regulated and the persons treated are not unduly debilitated, it is a perfectly safe drug.

It is excreted mainly through the lungs and the kidneys. Large doses may cause albuminuria.

Contra-indications.—Pregnancy, as it increases uterine contraction; advanced cases of heart disease and chronic

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nephritis. Should be used with caution and in small doses when the heart, liver or the kidneys are disordered.

Tetrachlorethylene.—It has the same action as carbon tetrachloride but is a little more efficacious and less toxic. Alcohol does not increase its toxicity. It should be given in 1 mil doses every hour for three doses daily for three days. Three hours after the last dose on the third day a saline purgative (sodium sulphate) should be given.

For *ascaris* give a single dose of 10 ms. in the early morning after fasting followed after half an hour by a dose of brisk saline and no food should be given until the bowels move.

Dose.—1 mil. or 15 ms.

Hexylresorcinol is useful both for hook-worm and ascaris but is very expensive and is not suitable for mass treatment. Rigid precautions have to be taken before treatment, as it loses its effect when given after food. 0·5 to 1 grm. in capsules should be given on an empty stomach after a purgative the previous evening and no food should be given for four hours after the remedy. An after-purgative is not essential.

Class D: Anthelmintics for Thread-worms

Oxyuris.—These worms inhabit the cæcum and therefore rectal injections (*see* page 363) that are so largely used are not of much value except for removing the worms that have travelled down to the descending colon, sigmoid or rectum. It is probable that these often die out naturally, therefore re-infection of the fingers should be prevented. The female worms wander out of the anus at night and deposit eggs on the surrounding skin causing itching and a desire to scratch. The eggs are thus carried by finger nails to the mouth. Drugs used for hook-worms also help the passage of a large number of thread-worms.

GROUP XIII

DRUGS ACTING ON THE KIDNEYS

The kidneys help to maintain the normal composition of the fluids of the body by separating from the blood the waste products of nitrogenous metabolism and other organic and inorganic constituents which are present in excess and which are not required by the body or cannot be metabolised. They help to preserve the alkaline reserve of the body by eliminating the non-volatile acids formed in the metabolic process, the volatile acids (CO_2) being excreted by the lungs. They also maintain the osmotic pressure at a definite level by excreting the excess of water as occasion demands.

Since all substances eliminated by the kidneys are kept in solution, it is necessary that sufficient water should be available from the body. It is not possible to reduce the normal water content of the blood, and in order that diuresis may occur there must be an excess of water, however small in the blood, *i.e.* hydræmia must be present. The hydræmia however, is only temporary, for the excess of water passes from the vessels into the different tissues until the pressure becomes equal.

The fact that urea, uric acid, pigments, salts and water which constitute the bulk of the urine are not manufactured

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by the kidneys, makes these organs of special interest to the pharmacologist. Inasmuch as digestion, assimilation, metabolism and circulation affect the activity of the kidneys, the condition of the urine furnishes a key as to the manner in which the different organs are performing their respective functions.

A healthy man passes about fifty ounces of urine daily, which is acid in reaction and contains about 2.2 p.c. of urea, whereas the blood is alkaline in reaction and contains only 0.05 to 0.1 p.c. of urea. It is evident therefore that considerable change of the fluid takes place during its passage through the kidneys before it reaches the ureters.

The different parts of the kidneys perform different functions. The *glomerulus* helps the passage from the blood to the tubules of a large quantity of fluid of alkaline reaction containing urea, chloride, sulphate, phosphate, etc. The fluid undergoes further changes in the *convoluted tubules*, where its reaction becomes acid, and urea, uric acid and other nitrogenous substances are added by process of excretion, and the urine becomes more concentrated by the reabsorption of some of the water. Cushny holds that glomeruli act as ultra-filters and filter off a fluid containing all the non-colloidal constituents of the plasma, *i.e.*, all the abnormal constituents and most drugs.

The composition of the blood itself exerts considerable influence in the production of diuresis. The plasma proteins, by their tendency to bind water, exert an oncotic pressure which resists filtration of fluid. When the plasma proteins fall below a certain level increased transudation must result. Moreover the water-binding properties of the colloids are influenced by the *p*H of the blood, by certain crystalloids, and possibly by some of the hormones. Increased alkalinity within clinical limits tends to favour water retention, while acids tend to diuresis.

Other things being equal, the greater part of the watery portion of the urine is excreted from the glomeruli, and this depends upon the glomerular pressure and the amount of blood flowing through it. If the blood flows through the glomerulus at a low pressure, due to resistance to efferent vessels, or if there is any obstruction to renal veins, the secretion of urine is diminished, although the glomerular pressure may be high in the latter case. It is evident therefore that diuresis occurs only when there is a continuous and rapid flow of blood under certain amount of pressure through the glomerulus. The rate of blood flow through the kidneys depends upon the general arterial pressure, the condition of the kidney vessels, and the pressure in the veins. The capillary system of the glomerulus supplied by the vasa afferentia, and that of the tubules supplied by the vasa efferentia, are antagonistic to each other. When the vasa afferentia dilate and

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the vessels of the tubules contract, the pressure and the flow in the glomeruli increase, whilst that to the tubules will be less and *vice versa*.

It must not be supposed that the kidneys simply act as filters, inasmuch as they interpose a barrier in the way of excretion for any substance in the blood which can be of use to the tissues ; and if the amount of this substance in circulation does not exceed a certain limit, the kidneys do not excrete it. This rule applies to sugar, salt, hæmoglobin and biliary constituents, and like water are retained in the blood up to a certain limit by a corresponding regulation of their reabsorption by the tubules. Thus sugar is not excreted unless its concentration is above 0.18 p.c. in the blood, and only when this threshold is exceeded that these substances are excreted in the urine. These substances are termed *threshold substances*. On the other hand no such barrier exists to purely waste products, such as urea, uric acid, etc., and these are termed *no threshold substances*.

The mechanism of diuresis is still unsettled, although it is possible that the secretion of urine is controlled by chemical stimuli. Various foreign substances, even the normal constituents of blood, when present in sufficient concentration, stimulate in some way the kidney cells. It is probable that the increased amount of urine which follows the improvement of kidney circulation may be due to the presence of a greater amount of chemical stimuli and other substances which pass through the organ.

Diuretics are drugs which increase the flow of urine. Increased urine may represent an increased intake of water or may be the result of removal of fluid from the tissues. Diuretics may be classified as follows :—

I. *Those acting by increasing the number of glomeruli functioning at a given time.*—Although there are about two million glomeruli in the human kidney, Richards and his associates have shown that all of them do not function at the same time, since the capillaries dilate only in those that are active, the rest remain closed. Each glomerulus together with its tubules forms a renal unit, and diuresis depends upon the number of glomeruli functioning at a given time. **Caffeine** and **urea** are supposed to act in this way, thus increasing the filtering surface.

II. *Those acting by increasing the flow of blood through the kidney or by raising the glomerular arterial pressure.*—The secretion of urine is largely proportional to the glomerular pressure and the rapidity with which the blood flows through the kidneys. Thus when there is congestion of the renal veins as in failure of compensation, the secretion is diminished, and improvement of circulation by increasing the action of the heart produces diuresis, *e.g.* by drugs of the **digitalis** group, **pituitary extract**, **adrenaline**, **caffeine**, **alcohol**, **ether**, etc. Dilatation of renal vessels as by the use of **spirit of nitrous ether** also causes diuresis.

Accumulation of fluid in the abdominal cavity mechanically hinders the outflow through the renal vessels, and removal of fluid, either by tapping or by purgation, removes venous stasis and produces diuresis.

The glomerular pressure may also be increased by making the

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blood hydræmic, as (1) by drinking large amount of water, and (2) by injecting **normal saline solution**, either subcutaneously, intravenously, or into the rectum.

III. *Those acting by causing acidosis.*—It has been found that large doses of **ammonium chloride** and **calcium chloride** cause reduction of the alkaline reserve of the plasma and act as diuretics. They increase the non-colloidal constituents of the blood plasma and by reducing the concentration of the plasma proteins help diuresis. **Sodium chloride** also acts in this way.

IV. *Those acting locally on the kidneys.*—Moderate irritation dilates the renal arterioles and raises the glomerular pressure, while the pressure in the arterial system generally and the resistance in the renal veins, remain unchanged. They stimulate the kidney cells and produce diuresis either by increasing the tubular secretion or by diminishing tubular reabsorption. These are also known as *irritant diuretics.* Except caffeine and its allies most of them irritate the kidney cells causing congestion and even nephritis when given in large doses. They are :—

(*a*) Glycosides: these are related to the aromatic series, **broom** (scoparin), **cantharidin.**

(*b*) **Acids, alkalies** and some salts, **caffeine, theobromine** and other **purin derivatives, calomel, novasurol, salyrgan.**

(*c*) *Certain volatile oils.*—Buchu, oils of juniper, copaiba and sandal wood.

V. *Those acting by salt action.*—These act by lessening viscidity of the blood, thereby increase the filtrability and raise the glomerular pressure. They also prevent reabsorption from the tubules. The effect is proportional to the osmotic pressure which they exert. **Water, urea, salts, sugar, milk** and **thyroid extract** act in this way.

Therapeutics.—The diuretics are indicated to remove either water or solids from the body, and have the following uses :—

(1) Cardiac and pulmonary disorders where the quantity of urine is diminished, or there is chance of dropsy.

(2) To hasten the elimination of waste products or poisonous materials circulating in the blood.

(3) Conditions where there is accumulation of fluid in some natural cavities of the body, as in ascites and pleurisy.

(4) To dilute the urine in inflammation of the bladder and urethra to make it less irritating, and in cases with a tendency to formation of calculi or deposition of solids.

Reaction of the urine.—The normal reaction of human urine is slightly acid with a *p*H range from 5.12 to 7.46, with an average of 6.03. During digestion when the gastric secretion is increased and during fasting the acidity becomes less.

The reaction becomes altered or may be highly acid by the use of mineral acids, but in practical therapeutics their usefulness is limited owing to their local irritant effect. The urine can be made acid by the use of acid salts, like acid sodium phosphate, or by the use of ammonium or calcium chloride, benzoic acid, boric acid and salicylic acid.

We have however more powerful means of making urine alkaline. The salts of sodium, potassium, lithium and calcium which are oxidised in the blood as carbonates and are eliminated as such by the kidneys render the urine alkaline.

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Those salts of ammonium that are eliminated as urea have very little effect in making the urine alkaline.

Urinary lithontriptics.—These are remedies employed for dissolving any concretions or calculi formed in the urinary tract or for preventing the deposition of solids from the urine. Alkalies are used in uric acid and oxalate of lime calculi. Benzoates are used when the urine is undergoing alkaline decomposition and phosphatic calculi are liable to be formed.

CLASS A: Diuretics

Water, Caffeine, Theobromine and Sodium Salicylate, Theophylline and Sodium Acetate, Urea, Oil of Juniper, Scoparium, Apocynum (*see* page 270), **Novasurol, Salyrgan, Spiritus Ætheris Nitrosi** (*see* p. 290), **Punarnava.**

AQUA DESTILLATA

Distilled water

Source and characters.—Prepared by the distillation of potable water. A clear, colourless, odourless and tasteless liquid.

AQUA STERILISATA

Sterilised Water

Source.—Distil potable water in a previously *sterilised* glass receiver and transfer the freshly distilled water to a sterilised hard glass container. Close the container to exclude bacteria, and sterilise by *heating in an autoclave*, or by boiling for thirty minutes.

N.B. It should be used within one month of its preparation. If opened the container may be closed again and sterilised as above.

PHARMACOLOGY OF WATER

Water forms about 64 p.c. of the body weight and the daily loss from the system is about 100 oz. It is necessary to compensate for the losses caused by the excretory organs and for the repair of the various fluids, and of the solid organs of the body into whose composition it enters. The demand for water is indicated by thirst and an insufficient supply will lead to disturbances of circulation and the heat regulating mechanism and to retention of the products of metabolism.

Water is not absorbed through the unbroken skin, although the epithelial cells slowly absorb it and eventually swell up. Application of cold water causes constriction of the cutaneous vessels and stops perspiration, while hot water dilates the vessels, helps radiation of heat, increases perspiration and lowers temperature. Cold sponging reduces temperature by abstraction of heat. Application of cold water to the body reflexly stimulates coughing and increases inspiratory efforts.

Internally.—Water is very slowly absorbed from the stomach, the normal epithelium of the stomach is scarcely

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permeable to water. It passes rapidly into the duodenum and is absorbed from the intestine. A large portion is passed out with the stool. When taken mixed with alcohol or carbon dioxide (aerated water) it is absorbed more freely by the stomach.

Taken in moderation it increases salivary, gastric, biliary and pancreatic secretions and helps digestion. As it helps better absorption of foods, less material is left in the gut for putrefactive bacteria. Taken in large doses it causes vomiting, while hot water slowly sipped is a valuable gastric sedative and antiemetic.

Kidneys and skin.—Drinking large quantities of water causes hydræmia and acts as a diuretic. It is a common experience to observe increased perspiration and urine when more water is given, and this in proportion to the amount of water consumed. In fact water is the only **diuretic** and almost all diuretics act by supplying the kidney more water, *i.e.*, by making the blood passing through the kidney vessels hydræmic. Drinking of water is accompanied by increased flow of blood and lymph which washes out from the body effete materials and toxins. Injected into the blood pure water has a tendency to cause hæmolysis by breaking up some of the less resistant blood cells.

Metabolism.—Water flushes the salts and different products of metabolism out of the system. During its passage through the blood and tissues pure water decreases osmotic pressure, and by internal exchange of salt and water between the blood and tissues, and by eliminating the excess material by the kidneys it helps to keep the composition of the blood constant. Nitrogen elimination is increased chiefly in the form of urea, and the sulphates and phosphates are also increased.

Therapeutics of Water

Externally.—Besides its uses already adverted to in pages 37-40, water, in the form of ice, or constantly changed through a Leiter's coil, is useful in subduing many acute inflammatory diseases, such as meningitis, cerebritis, synovitis, sprains, etc. It contracts not only the superficial blood-vessels, but also those of the organs by reflex action. On the same principle, a local application of ice to the surface arrests internal hæmorrhages, such as epistaxis, hæmatemesis, etc. A sudden partial application of cold to the abdomen, by flapping a wet towel over it, excites contraction of the parturient womb, and is therefore employed in uterine inertia and post-partum hæmorrhage. A smart sprinkling of cold water on the face restores consciousness in hysteria, fainting and narcotic poisoning. The same plan may be adopted in reviving still-born infants. Iced water

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subcutaneously injected over the diaphragm checks hiccough, and within paralysed muscles improves their nutrition. Ice poultice applied to the chest is used in the treatment of pneumonia. Hot water used as an intra-uterine douche arrests post-partum hæmorrhage.

Internally.—The sucking of ice allays thirst, vomiting and hiccough. A small glass of cold water slowly sipped controls the craving for drinks by stimulating the circulation. In the same manner hot water before meals soothes the irritable condition of the stomach in gastritis, gastrodynia and gastric ulcer. A glass of cold water taken immediately on rising from bed helps the bowels to act. The swallowing of ice arrests hæmatemesis. Copious draughts of water help to wash out minute deposits of **urinary gravel**. If it is a uric acid calculus, drinking of distilled water diminishes the tendency to deposition. As a diuretic Glaessner advocates the oral administration of distilled water for uræmia, hypertension without arteriosclerosis, and urinary lithiasis. Large draughts of water given between meals may arrest the formation of gall-stones by liquefying the bile. As an *emetic*, warm water should not be given in quantities sufficient to over-distend the stomach, as this may paralyse the muscles and thereby impede rather than promote vomiting. Half to one pint at a time is enough for the purpose. In œdema water is only a safe diuretic when the salt intake is limited. On the other hand its restriction is helpful in acute nephritis and cardiac œdema when the renal circulation fails to deal with normal quantities of fluid. The intake of water should be gradually increased as the kidneys show evidence of being able to deal with it.

CAFFEINA

Caffeine. $C_8H_{10}N_4O_2,H_2O$

Syn.—Theine; Guaranine.

Source.—An alkaloid obtained from the dried leaves of *Camellia sinensis*, or from certain other plants: or may be prepared synthetically. It is 1 : 3 : 7-trimethylxanthine.

Tea yields 3 to 5 p.c., coffee seeds 1.3 p.c., guarana 5 p.c., *maté* or Paraguay tea 0.5 p.c., kola nut 3 p.c.

Characters.—Colourless, silky, needles; odourless; taste, bitter.

Solubility.—1 in 80 of cold, and easily in boiling water, alcohol and chloroform. The aqueous solution is neutral.

Incompatibles.—Tannic acid, potassium iodide and mercurial salts.

B.P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

CAFFEINA ET SODII BENZOAS

Caffeine and Sodium Benzoate

Source.—Prepared by mixing caffeine with an equal weight of sodium benzoate. Contains not less than 47 p.c. and not more than 50 p.c. of anhydrous caffeine, and not less than 50 p.c. and not more than 53 p.c. of sodium benzoate.

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Characters.—A white powder; odourless; taste, slightly bitter. *Soluble* in 1 part of warm water; completely in 4 parts of water, slightly in alcohol (90 p.c.).

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.; or 2 to 5 grs. or 0.12 to 0.3 grm. (by injection).

Non-official Preparations

1. **Caffeine-Chloral.**—Granular crystals. Soluble. Analgesic and laxative. Hypodermic injections useful in *constipation*, *rheumatism*, *sciatica*. *Dose.*—3 to 8 grs. or 0.2 to 0.5 grm.

2. **Migrainine.** *Syn.—Antipyrin Caffeine-citricum.*—Soluble in water; contains 9 p.c. caffeine, 1 p.c. citric acid, and 90 p.c. phenazone. In *headache*, but causes sleeplessness. *Dose.*—8 to 15 grs. or 0.5 to 1 grm.

3. **Caffeina et Sodii Salicylas.**—Evaporate to dryness Caffeine 5, Sod. Salicylas 6, Water 20. A white amorphous powder containing 47 to 50 p.c. of caffeine. Acts like digitalis, but more rapid. *Dose.*—5 to 15 grs. or 0.3 to 1 grm. by mouth 2 to 5 grs. or 0.12 to 0.3 grm. hypodermically.

4. **Caffeinæ Citras.**—White inodorous powder with an acid reaction. Soluble in 32 parts of water. *Dose.*—2 to 10 grs. or 0.12 to 0.6 grm.

5. **Iodo-Caffeine.** *Syn.—Sodium-Caffeine Iodide.*—A white powder, slightly soluble in cold water and freely in warm water. Contains 65 p.c. caffeine. A valuable diuretic in *cardiac dropsy* and *pleurisy*. Useful in *asthma*. *Dose.*—2 to 10 grs. or 0.12 to 0.6 grm.

Pharmacology

Internally.—Caffeine has three important actions, *viz.*, (1) it is a diuretic; (2) it excites the higher nervous centres; (3) it acts on all muscle-fibres, whether cardiac, striped or plain.

Heart and circulation.—In medicinal doses it slows the pulse from **stimulation of the inhibitory centre** and increased vagus excitability. Frequently however no change in the pulse-rate is observed. In some cases the stimulation of the heart is pronounced possibly due to increased flow through the dilated coronary arteries. In toxic doses the pulse becomes very frequent, irregular and intermittent, and at last the heart stops in systole. These effects are largely due to the direct action of the drug on the cardiac muscle, chiefly the nodal tissue and the bundle of His, and partly on the cardio-inhibitory centre. The vaso-constrictor centre is moderately stimulated causing a rise of blood-pressure; on the other hand there is peripheral vaso-dilatation which overcomes the effect of constriction.

An injection of caffeine and sodium benzoate usually causes a slight slowing of the pulse without any appreciable effect on the arterial pressure. But this often induces undesirable nervous symptoms which precludes it from being used repeatedly without risk of over stimulating the brain and cord. It has no effect on arteries not under control of the vaso-constrictor centre. The coronary arteries are dilated.

Respiration.—In therapeutic doses given by the mouth the respiration is moderately stimulated, sometimes however it is scarcely affected unless cardiac dyspnœa is improved

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by the circulatory effect. The respiration is definitely stimulated when given as an injection.

Temperature is not affected by small doses but is increased by large doses.

Nervous system.—Caffeine in small doses acts entirely on the **higher psychical centres**, this being the only part really affected, hence there is mental exhilaration and removal of fatigue and languor. It has been shown that there is an increase in both the rapidity and accuracy of purely intellectual processes ; but caffeine has no effect on those forms of cerebral activity which require a combination of mental processes with physical co-ordination. The perceptions become more acute, pain is more keenly felt, and the sense of touch becomes more discriminating. In larger doses it stimulates the motor area as evidenced by restlessness, wakefulness, ringing in the ears, delirium and tremors.

Medulla and cord.—It stimulates the **respiratory centre** and slightly the **vaso-constrictor** and **vagus**. The motor cells of the cord are also stimulated with acceleration of the passage of impulses like strychnine, but more mildly. It therefore, increases the reflex activity and improves the tone of the muscle.

Muscle.—Its action is well marked on voluntary muscles. A moderate dose will directly increase the strength and irritability of the muscle ; and the total amount of work done before exhaustion is increased. Considering the universal use of beverages containing caffeine it is of practical importance to know that as a result of human experiments with ergograph the increase in muscular power is not followed by a compensatory depression.

Metabolism.—The effect of caffeine on metabolism is not clear. It increases the excretion of xanthine and urea, consumption of oxygen and elimination of CO_2. There is some rise of temperature due to increased muscular activity and effects on the nervous system.

Kidneys.—Caffeine is a powerful **diuretic** and it has been found that under its use the kidney vessels are dilated while causing general vaso-constriction thus increasing the filtration pressure in the renal vessels. But since it acts as a diuretic in the isolated kidney just as well as in the intact animal, the diuresis cannot be due to circulatory changes. On the other hand the evidence is strong that the effect is due to direct stimulation of the renal epithelium, and that the increased flow of blood is the result and not the cause of increased function (Cushny). Verney (*Quarterly Journal of Pharmacology*, 1928) asserts that it acts by increasing the number of glomeruli functioning thus increasing the filtration surface. The extent of diuresis varies with the amount of water in the body ; and the urine is of low specific gravity.

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the urinary solids being less than the watery portion of the urine, *i.e.*, the diuresis depends upon the amount of filtrable fluid available in the body and becomes less when the accumulated fluid is eliminated and the body becomes relatively "dry". In other words diuresis depends upon an increase of the non-colloidal constituents of the blood which by reducing the osmotic resistance to filtration allows more fluid to pass through the glomeruli into the tubules. It has been found that on a salt-free diet sodium chloride almost disappears from the urine as it is reabsorbed to maintain an adequate concentration of salt in the blood. If however caffeine is administered the salt reappears in the urine. It has therefore been suggested that caffeine *interferes with the reabsorption of salt* by the tubules, as a result of which more salt remains in the tubules which exerts an osmotic pressure and hinders reabsorption of fluids. Moreover there is increased permeability of glomerular cells which allow of increased filtration through them.

As a diuretic caffeine is inferior to theobromine and theophylline, and of these theophylline acts more powerfully on the kidney. Caffeine however does not injure the kidneys when used for a prolonged period even in large doses. It has therefore the advantage over other diuretics and causes no further damage to the kidneys when used in renal disorder.

Absorption and elimination.—Caffeine is rapidly and completely absorbed, only a very small percentage being eliminated in the urine, and none appears in the stools even when given in large doses. About 80 p.c. is completely oxidised into urea, the rest being excreted in the urine as di- and mono-methylxanthine. When used for a long time a certain degree of tolerance is produced so that diuresis is not so marked after some time.

Acute toxic action.—Burning in the throat, thirst, gastro-intestinal pain, violent vomiting and purging, giddiness, tremors in the extremities; free diuresis, clear intellect were observed in a case of poisoning by 60 grs. of the citrate; recovery took place under the use of nitroglycerin.

Chronic toxic action.—A slow development of the toxic symptoms from excessive tea-drinking is very rare, but is well illustrated in the case admitted into the Belleveue Hospital, New York. Thirty cups per day without food were drunk by him when he got awfully prostrated. Extreme indigestion, extreme anæmia, complete inability to move, great cardiac and respiratory distress were the chief symptoms. In another case symptoms of posterior and lateral sclerosis of the cord were marked.

THERAPEUTICS

Externally.—An infusion of tea is often used as a collyrium in simple conjunctivitis, and a gargle for sore-throat.

Internally. **Heart.**—As a *cardiac stimulant* it is chiefly used as an emergency drug and should not be repeated frequently. As it does not possess the permanent tonic action

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of digitalis, it cannot replace that drug, but may usefully be used as an adjuvant when a greater effect is desired. It tones up the heart and removes the intermittent character of the pulse brought on by large doses of *Apocynum cannabinum*. It is of signal service in cardiac dropsy specially when combined with digitalis. It may be used to strengthen the heart in many acute diseases, such as pneumonia, fevers, etc. Because it dilates the coronary vessels and relieves vascular spasm, theobromine is used in angina.

Lungs.—As a **respiratory stimulant** caffeine may be used in œdema of the lungs and depression of respiration. Hot black coffee is largely used in narcotic poisoning to stimulate the respiratory centre. Sometimes it relieves the paroxysms of asthma.

Nervous system.—In migraine caffeine or the citrate, in combination with aspirin, phenacetin, etc., to assist their action and to prevent their depressing effect on the heart, are sometimes useful. On the other hand Hale has shown that the toxicity of antifebrin and phenacetin is increased by combination with caffeine. Owing to its action on the central nervous system it is used in nervous exhaustion and as it stimulates the brain and respiratory centre it is used in alcoholic poisoning.

Kidneys.—Caffeine is an uncertain diuretic and has now been superseded by diuretin, agurin and theophylline, but these tend to cause gastric irritation, nausea and vomiting. It is largely used in cases of **cardiac dropsies**, and is of value as a preliminary to digitalis treatment. Its value is not so certain in renal and hepatic dropsies. In chronic parenchymatous nephritis there is as a rule very little response, while in chronic interstitial nephritis it usually gives better results. Many patients get habituated to its use and its diuretic action is entirely lost on them after a week or so. On account of its stimulating action upon the kidney cells caffeine *should not be given* in cases of *acute nephritis*.

Prescribing hints.—Caffeine is usually given alone but it may be combined with other drugs, such as strychnine or digitalis as they mutually help each other, or it may be exhibited alternately with digitalis. It should be remembered that the citrate is acid, and when dissolved in water forms an acid solution and dissociates free citric acid. It is therefore incompatible with substances which cannot be prescribed with acids. With iodides it liberates iodine. As an emergency drug caffeine sodium-benzoate should be used hypodermically. When caffeine is used as a circulatory stimulant it stimulates the cerebral cortex, and a few doses may cause excitable nervous condition with wakefulness when sleep may be of the greatest value to the patient. As it stimulates perception it may increase the patient's suffering.

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THEOBROMINA ET SODII SALICYLAS

Theobromine and Sodium Salicylate

Syn.—Diuretin.

Source—It is a mixture of sodium theobromine and sodium salicylate in approximately molecular proportions. Prepared by the interaction of sodium hydroxide, theobromine, and sodium salicylate. Contains not less than 46 p.c. of theobromine, 41 p.c. of sodium salicylate, and 6.9 p.c. of sodium.

Characters.—A white, amorphous powder. No odour; taste, sweetish and alkaline. *Solubility.*—In equal parts of water. Insoluble in alcohol (90 p.c.), in ether and in chloroform.

B.P. Dose.—10 to 20 grs. or 0.6 to 1.2 grm.

THEOPHYLLINA ET SODII ACETAS

Theophylline and Sodium Acetate

Syn.—Theocin Sodium Acetate.

Source.—Prepared by dissolving equimolecular proportions of sodium theophylline and sodium acetate in water, and evaporating to dryness. Contains not less than 55 p.c. of anhydrous theophylline.

Characters.—A white, crystalline powder; odourless; taste, bitter. *Soluble* in 25 parts of water, insoluble in alcohol (90 p.c.), in ether and in chloroform. Solution alkaline to litmus.

B.P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

Non-official Preparations of Theobromine and allied Purin Derivatives

1. **Theobromina et Sodii Acetas.** *Syn.—Agurin.*—A deliquescent powder, easily soluble 1 in 2 of water. *Dose.*—10 to 15 grs. or 0.6 to 1 grm.

2. **Theophylline, U.S.P.** *Syn.—Theocin.*—In white, odourless crystalline powder, isomeric with theobromine. Taste, bitter. Soluble 1 in 160 of water, readily in hot water. *Dose, U.S.P.*—0.25 grm. or 4 grs.

3. **Iodo-theobromine.** *Syn.—Theobromine Sodium-Iodo-Salicylate.*—Contains 40 p.c. of theobromine in combination with sodium iodide and salicylate. In *cirrhosis of the liver, acute nephritis. Dose.*—2 to 10 grs. or 0.12 to 0.6 grm.

4. **Theobromina.** *Syn.—Dimethylxanthine.*—Isomeric with theophylline. An alkaloid obtained from the seeds of Theobroma cacao. *Dose.*—5 to 10 grs. or 0.3 to 0.6 grm.

5. **Theobromine Calcium Salicylate.** *Syn.—Calcium Diuretin*; *Theocalcine.*—Contains 48 p.c. theobromine and 11 p.c. calcium salicylate. A white powder sparingly soluble in water. Action like diuretin. Useful in *arterio-sclerosis* and *asthma. Dose.*—7 to 15 grs. or 0.5 to 1 grm.

6. **Euphyllin.**—*Theophylline Ethylenediamine.* Yellowish crystals, freely soluble in water. Causes vaso-dilatation and hydræmia of the kidneys. Diuretic in cardiac and renal dropsies, arteriosclerosis, angina and cardiac asthma. *Dose.*—3 grs. or 0.2 G. by mouth or subcutaneously.

7. **Rhodan-Calcium-Diuretin.**—In tablets, each contains calcium-diuretin 7½ gr. and pot. sulphocyanate 1½ gr. *Dose.*—One tablet twice or thrice daily after food.

Pharmacology and Therapeutics of Diuretin and other Purin Derivatives

These substances are called purin derivatives because they are derived from xanthine, one of the purin bases, by the substitution of a certain number of methyl atoms (CH_3) for atoms of hydrogen. These are therefore closely related to uric acid.

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These derivatives are powerful diuretics without any side-effects on the nervous system as possessed by caffeine. They however irritate the stomach and produce nausea and vomiting. Attempts have therefore been made to avoid these unpleasant symptoms and also to enhance their action by combining them with calcium, luminal, etc. Theophylline and sodium acetate is more powerful and is more liable to upset the stomach than theobromine and its salt.

These closely allied substances differ in their therapeutic action. Caffeine stimulates the heart and has only a slight direct action on the kidneys. Theobromine acts much more powerfully on the renal epithelium, and stimulates the heart and lowers blood-pressure, dilates coronary vessels and relieves vascular spasms.

Theocin is a less powerful cardiac stimulant than caffeine but it is a more active diuretic than either of the other two. The best results are obtained with theocin in chronic interstitial nephritis where there is always sufficient healthy kidney tissue left to respond to the drug. It is *contra-indicated in acute nephritis and in diffuse parenchymatous inflammation.* In cases where the kidney is embarrassed by either local or general obstruction theocin and theobromine only act after the obstruction has been relieved by digitalis. This is an important point to bear in mind. All these diuretics, but specially theocin, increase the solid constituents as well as the water. This places theocin amongst the most efficient of diuretics in cases of œdema with retention of sodium chloride.

Theobromine is usually given either as the double salt with sodium salicylate (*diuretin*), or with sodium acetate (*agurin*). Agurin is free from most of the unpleasant side-effects of diuretin, especially the depressing action of the salicylate, while the diuretic action is somewhat increased, since the acetate itself possesses diuretic properties and the amount of theobromine contained in agurin is 10 p.c. more than in diuretin. It is most successful in cases of dropsy due to myocardial degeneration, complicated with nephritis and even in uncomplicated cases.

Theocin is a very powerful diuretic and often acts where both of the above-mentioned combinations have failed; it may either be given alone, or in the form of theophylline-sodium acetate. It is very prompt in its action but the effects soon pass off and it cannot therefore be administered continuously for any length of time. It also produces certain unpleasant side-effects which should be carefully borne in mind. These effects are as follows:—

(1) Symptoms of gastric disturbance; vomiting and diarrhœa.

(2) Nervous symptoms; headache, vertigo and convulsions.

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These effects are most likely to occur when pure theophylline is used ; hence the compound salts should be used in preference, and the following precautions should be observed :—

(1) The daily dose should not exceed a total of 15 grs.

(2) The drug must always be freely diluted and given on a full stomach.

(3) It should only be given on alternate days, using either diuretin or agurin on the intervening day.

(4) If the patient develops headache or sickness, the drug should be stopped immediately.

(5) Never use theophylline if there be acute nephritis or excessive destruction of kidney substance. Remember that it only acts when there are healthy kidney cells for it to act upon.

UREA

Urea. $CO(NH_2)_2$

Syn.—Carbamide.

Source.—Prepared from ammonium cyanate. It is diamide of carbonic acid.

Characters.—Colourless, transparent, prismatic crystals ; no odour ; taste, saline, cooling. *Soluble* in 1 part of water, in 5 parts of alcohol (90 p.c.), insoluble in ether and in chloroform.

B.P. Dose.—15 to 240 grs. or 1 to 16 grm.

Non-official Preparation

1. **Quininæ et Urea Hydrochloridum, U.S.P.** *Syn.—Urea Quinine.*—Contains 58 p.c. quinine. In colourless, trauslucent prisms. Soluble in water. Used hypodermically in *malaria* and for local *anæsthesia*. *Dose, U.S.P.*—Hypodermic, 1 grm. or 15 grs. (one dose only).

Pharmacology and Therapeutics

Urea is rapidly absorbed from the intestine and acts as a powerful **diuretic** by preventing normal reabsorption of water by maintaining the osmotic tension of urine. Since it is rapidly excreted its effects are of very short duration. It is used in the treatment of dropsy. Miller and Feldman treated **cardiac dropsy** with massive doses of urea (2.5 to 6 dr.) thrice daily in 40 p.c. solution with very good results. Some fruit juice is added to cover the taste. When about 50 grm. were given daily most of the œdema disappeared. Some cases regained their cardiac efficiency without the use of digitalis (*British Medical Journal*, Jan. 21, 1933). Because of its property of dissolving uric acid calculi it has been recommended as a preventive and cure for this trouble. As a diuretic it is used in cirrhosis of the liver, gout and chronic kidney diseases.

It is not utilised in the body, and when given in larger doses it is entirely eliminated by the kidneys. Since its

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elimination is impaired in chronic interstitial nephritis and not in chronic parenchymatous nephritis, it is used as a diuretic in the latter condition. In combination with quinine (urea quinine) it is used as a local anæsthetic, as a substitute for cocaine, in 1 p.c. solution. It is non-toxic, soluble in water, and can be sterilised. A 5 to 10 p.c. solution has been injected between the vein and the mucous membrane of the rectum in *internal piles*.

It is supposed to be a true galactogogue.

It is largely used for testing the efficiency of the kidneys, for which purpose 15 grms. are given by the mouth and its excretion determined at suitable intervals. Figures below 1.5 p.c. collected one hour after and 2 p.c. after two hours show a poor concentrating power of the kidneys and indicates renal inefficiency. Normal kidneys may concentrate up to 4 p.c. or over.

OLEUM JUNIPERI

Oil of Juniper. *(Not official)*

Source.—The oil distilled from the ripe fruit of *Juniperus communis*, and rectified. Colourless or pale greenish-yellow; odour characteristic; taste, aromatic bitter. *Solubility.*—1 in 4 of alcohol (95 p.c.).

Composition.—Contains (1) *Pinene* ($C_{10}H_{16}$), *Camphene* ($C_{10}H_{16}$), Terpinenol and Cadinene ($C_{15}H_{24}$). (2) Juniper camphor, a crystalline body.

Dose.—½ to 3 ms. or 0·03 to 0·2 mil.

Non-official Preparation

1. **Spiritus Juniperi.**—1 in 10. *Dose.*—5 to 20 ms. or 0·3 to 1·2 mils.

Pharmacology

Oil of juniper resembles oil of turpentine in its action, but it is a more powerful **renal stimulant** and **diuretic**, and is more agreeable to the stomach. In large doses, it excites the genital organs like cantharidin, causing strangury and priapism. It is absorbed into the blood and is excreted with the urine, to which it imparts an odour of violets. The diuretic effect is observed in dropsy, whilst in health it is said to diminish the urine secreted.

Therapeutics

Sometimes it is used as a stomachic, stimulant and antispasmodic, but it is chiefly employed as a diuretic in cardiac and hepatic dropsy, and in chronic nephritis. It should not be used in acute renal affections. It is best given with salines. Gin and Hollands contain it and they can be used as alcoholic beverages in the above diseases.

SCOPARIUM

Broom Tops. (*Not official*)

Source.—The fresh and the dried tops of *Cytisus scoparius*.

Composition.—(1) *Scoparin*, a yellow crystalline substance. (2) *Sparteine*, a liquid volatile alkaloid. (3) *Genisteine*, a crystalline volatile alkaloid. (4) *Sarothamnine*, a non-volatile alkaloid.

Non-official Preparations

1. **Infusum Scoparii Recens, B.P.C.**—Made with *dried* tops. 1 in 10. *Dose.*—1 to 2 ozs. or 30 to 60 mils.
2. **Succus Scoparii.**—Made with *fresh* tops. *Dose.*—1 to 2 drs. or 4 to 8 mils.

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Broom because of scoparin acts as a valuable **diuretic.** It is usually prescribed with other diuretics in all forms of **dropsy** especially cardiac, and interstitial nephritis. Haustus Scoparii Compositus, consisting of Potassium Tartrate 20 grs., Sp. Juniperi 30 ms. and Infusum Scoparii Rec. ad 1 oz., is a very valuable combination, but it should never be prescribed for acute Bright's disease.

For action of Sparteine, *see* page 241.

Class B : Urinary Antiseptics

In order that a drug may act as a genito-urinary antiseptic it must be absorbed through the alimentary canal and excreted by the kidneys. Many antiseptics are however eliminated in an inactive form and are therefore useless as genito-urinary antiseptics. But the drugs of this group are of special value in disinfecting the genito-urinary tract during their elimination in more or less concentrated form. The continual excretion of these drugs through this channel reduces the number of organisms in the urine and prevents sepsis. The action of genito-urinary antiseptics largely depends upon the reaction of the urine which considerably influences the growth of bacteria in the urine. Thus it has been shown that although normal urine undergoes putrefaction in about 36 hours, it takes only 24 hours if rendered alkaline by the administration of potassium salts. On the other hand it takes three days to putrefy if it is rendered acid by the administration of acid sodium phosphate.

The commonly used urinary antiseptics are :—

1. Ammonia Formaldehyde Group
   Hexamine, Helmitol, Hexyl-resorcinol
2. Coal Tar Group
   Benzoates, Salicylates, Salol, Mercurochrome, Acriflavine, Methylene Blue
3. Boric Group
   Boric Acid and Borax
4. Essential Oils
   Copaiba, Sandal Wood Oil, Buchu

Besides these, certain drugs are used as adjuvants, *e.g.*, the citrates when given in sufficient doses render the urine alkaline, and acid sodium phosphate increases the acidity of urine.

HEXAMINA

Hexamine. $C_6H_{12}N_4$

Syn.—Methenamina ; "Urotropine" ; Aminoform ; Formin.

Source.—Obtained by the combination of ammonia and formaldehyde. Contains not less than 99 p.c. of pure hexamethylenetetramine.

Characters.—Colourless crystals or crystalline powder. Inodorous. Taste, at first sweetish, afterwards bitter. *Solubility.*—1 in 1½ of water and 1 in 8 of alcohol (90 p.c.). Solution alkaline to litmus.

B.P. Dose.—10 to 30 grs. or 0·6 to 2 grm.

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Non-official Preparations

1. **Piperazin.** *Syn.—Diethylene-diamine.*—Formed by the action of sodium glycol on ethylene diamine. In small colourless deliquescent crystals, with a strongly alkaline reaction, saline taste and faint odour. Soluble 4 in 7 of water. In uric acid diathesis, gout and lithiasis. *Dose.*—5 to 15 grs. or 0.3 to 1 grm.

2. **Hexamine Glycocholate.** *Syn.—Felamine.*—As cholagogue and biliary antiseptic. In *catarrhal jaundice*, after-treatment of typhoid fever and in gall-stones. *Dose.*—5 grs. in tablets.

3. **Helmitol.** *Syn.—Formamol*; *New Urotropine.*—A citrate combination of urotropine and formaldehyde. A more powerful antiseptic than urotropine and never causes irritation of the urinary apparatus. *Dose.*—7½ to 15 grs. or 0·5 to 1 grm.

4. **Hexyl-Resorcinol.** *Syn.—Caprokol.*—1 : 3 Dihydroxy 4-Hexylbenzol. The introduction of an alkyl radical to resorcin markedly decreases the toxicity and at the same time increases its germicidal activity. A valuable *urinary disinfectant.* It does not irritate the urinary tract, and the germicidal action is not modified by the natural range of the reaction of the urine, but it is destroyed by the use of large doses of bicarbonate of soda. Valuable in *cystitis* and *pyelitis.* Produces local necrosis when given hypodermically. *Anthelmintic* for hook-worm (*see* page 369). *Dose.*—2 to 10 grs. or 0·12 to 0·6 grm.

5. **Pyridium.** *Syn.—Malophen.*—Phenyl-azo-alpha-diamino-pyridine hydrochloride. A brick red crystalline powder, slowly soluble in cold water, glycerin, alcohol, etc. A *powerful bactericide* in gonococcal and staphylococcal infections of the genito-urinary tract. Useful in gonorrhœal infection and complications of males and females, pyelitis and cystitis. *Dose.*—Each tablet contains 1½ gr. or 0·1 grm. Two at a time after meals.

Pharmacology and Therapeutics

Hexamine is rapidly absorbed and appears in the urine about an hour after administration. The quantity appearing in the urine varies with its absorption, about 20 to 30 p.c. being decomposed in the stomach during digestion, but only about 1 p.c. during fasting when the contents are feebly acid. If used for a prolonged period a concentration of 1 in 2000 can be obtained with a dose of 0.67 grm. It is doubtful whether when administered *per os* it forms enough formaldehyde to retard the growth of bacteria in the urinary tract, for cultures of urine show growth of organisms during hexamine treatment.

It is one of the most powerful **urinary antiseptics** we possess. But by itself it has no antiseptic power, and its value depends upon the formation of formaldehyde in the acid urine. When the urine is alkaline it should be rendered acid by the administration of acid sodium phosphate in 10 to 15 gr. doses, or of ammonium chloride 20 grs. four times a day, since more formaldehyde is liberated if the urine is kept acid. It has been recommended in typhoid fever not only to lessen the chance of cystitis but also to prevent the spread of infection. For the same reason it is largely used in B. coli infection of the urinary tract. In this condition the urine is already highly acid and the use of hexamine alone will render the urine sterile. Since acid urine irritates the urinary tract it is often desirable to use large doses of alkalies (citrates or acetates), to make the urine alkaline, and

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since the growth of colon bacillus is inhibited in an alkaline urine this will not only relieve irritation but will also prevent further growth of the organisms. Meantime hexamine may be exhibited to act as long as the urine remains acid. If the infection of the urinary tract is due to pyogenic cocci or putrefactive organisms, the urine becomes foul and alkaline, as in cases of cystitis, and it requires to be rendered acid for hexamine to act. In generalised infection with coli organisms hexamine given intravenously (20 to 40 p.c. solution, 2 to 5 c.c.) gives brilliant results. It has been used in infection of the gall-bladder, cerebral malaria, pyelitis of pregnancy and post-operative anuria when given intravenously. In the treatment of cholecystitis it should be given in large doses (60 to 100 grs.) with an equal quantity of bicarbonate of soda three times a day. In malarial coma 3 c.c. of a 40 p.c. solution given intravenously will cause the cerebral symptoms to pass off slowly although the parasites remain in the blood. Combined with antitetanic serum it has given remarkable results in tetanus. It has been suggested that hexamine facilitates the entrance of the antitoxin into the cerebro-spinal fluid. It enters the different organs and secretions freely and has been found in the bile, cerebro-spinal fluid and pancreatic juice. It has therefore been used in cerebro-spinal meningitis, poliomyelitis of children and various inflammatory diseases of the meninges and brain, although there is little evidence that hexamine is converted into formaldehyde in the bile or cerebro-spinal fluid. In fact Otto Mayer suggested the use of 10 c.c. of a 10 p.c. solution with 20 c.c. of air after lumbar puncture in meningitis. He has found good results following its use which he attributes to the hypertonic effect of the drug and not to any disinfectant action. In combination with sandal wood oil and methylene blue it is often used in gonorrhœa and gleet.

Since formaldehyde forms soluble compounds with uric acid, it has been used in gout, gravel, and uric acid diathesis, but the results have been disappointing. It is specially valuable as a prophylactic after catheterisation.

Hexamine itself is not irritant but formaldehyde irritates the bladder and in susceptible persons may cause painful micturition and eventually cystitis and even hæmaturia.

COPAIBA

Copaiba

Syn.—Balsam of Copaiba.

Source.—The oleo-resin obtained by incision from the trunks of various species of *Copaifera*.

Characters.—A more or less viscous liquid; generally transparent; sometimes opalescent or slightly fluorescent. Odour, peculiar, aromatic. Taste, acrid, somewhat bitter. *Solubility.*—Entirely in an equal volume of dehydrated alcohol.

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Composition.—(1) The *Volatile Oil*, 48 to 85 p.c. (2) The *Resin*, 15 to 52 p.c. which remains dissolved in the oil. The resin consists of (*a*) *Copaivic Acid*, a crystalline resin, and (*b*) a non-crystallisable viscid resin.

B.P. Dose.—10 to 30 ms. or 0·6 to 2 mils.

Non-official Preparations

1. **Copaiba Resin.** *Dose.*—10 to 20 grs. or 0·6 to 1·2 grm.
2. **Oleum Copaibæ.**—A colourless or pale yellow oil with the odour and taste of copaiba. *Dose.*—5 to 20 ms. or 0·3 to 1.2 mils.

Pharmacology

Internally. **Gastro-intestinal tract.**—It imparts an acrid nauseous taste, and a feeling of warmth to the epigastrium, and gives rise to disagreeable eructations. Continued long it causes dyspepsia and looseness of the bowels.

Mucous membrane.—The volatile oil and the resin are readily absorbed into the blood, and are excreted by the mucous membranes, particularly by the mucous surface of the genito-urinary and respiratory tracts, which they stimulate, producing an increased vascularity and increased secretion which, if foul, is disinfected. Thus copaiba is a disinfectant and expectorant, and a stimulating disinfectant to the genito-urinary surface. It imparts the odour of the drug to the breath, urine and mucous secretions.

Skin.—It is excreted by the sweat-glands, and acts as an irritant to the skin, producing sometimes an erythematous eruption known as "copaiba rash." A portion of it is also excreted by the milk to which it imparts its nauseous flavour.

Kidneys.—It powerfully **stimulates** the kidneys, perhaps more than any other drug containing either resins or volatile oils. It is therefore a powerful **diuretic.** This diuretic action is largely due to the resin, which during its excretion stimulates the secreting cells of the kidneys. Large doses cause **renal congestion,** with lumbar pain and scanty, bloody and albuminous urine. The resin and volatile oil are excreted in the urine which they disinfect.

It should be remembered that the resin is inferior to the oil as an antiseptic, but is a powerful **diuretic.**

Micro-organisms.—By disinfecting the secretion of the genito-urinary tract as well as by rendering the urine aseptic, copaiba decidedly acts as a poison to many infective micro-organisms, especially the gonococcus, which are destroyed by the oleo-resin as it passes out.

Therapeutics

Internally. **Mucous membrane.**—As a stimulating disinfectant to the mucous secretions, it has been found useful in vaginitis, cystitis, pyelitis, leucorrhœa and chronic bronchitis.

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Gonorrhœa.—On account of its *specific action on the gonococcus*, it is a very valuable remedy for gonorrhœa. It should be given when the acute symptoms have somewhat subsided in 15 to 20 m. doses, increasing it slowly, as it often upsets the stomach. Its effect is not so marked in gleet.

Kidneys.—As a *powerful diuretic*, both copaiba and its resin have been employed in dropsy, due either to hepatic or cardiac disorder. It is contra-indicated in Bright's disease.

Prescribing hints.—Copaiba may be given in capsules, pills, paste, or emulsion. Tincture of quillaia or solution of potash helps emulsification. Cinnamon water, peppermint water, tinctures of ginger and orange fairly cover its unpleasant smell. The oil is best given in capsules or suspended by mucilage. The efficacy of the drug is greatly increased if it is given with sandal-wood oil, cubebs oil, buchu, etc., as in the following prescription : ℞ Ol. Santal. Flav. 4 drs., Copaiba 1 oz., Liq. Potassæ 1 dr., Spt. Æther. Nitrosi 4 drs., Tr. Hyoscyam. 4 drs., Tr. Buchu 1 oz., Mucilage Acacia 1 oz., Ol. Cinnamomi 10 ms., Syrup to 6 ozs. Mix and make a creamy emulsion. *Dose.*—One dessertspoonful thrice daily after food.

OLEUM SANTALI AUSTRALIENSIS

Oil of Australian Sandal Wood

Source.—The oil distilled from the wood of *Eucarya spicata*, and rectified. Contains not less than 90 p.c. w/w of free alcohols, calculated as Santalol, $C_{15}H_{24}O$.

Characters.—A colourless, or pale yellow, oily liquid; with characteristic odour of the wood and unpleasant taste.

B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

OLEUM SANTALI

Oil of Sandal Wood

Syn. I.V.—*Chandaner tel*, Beng.

Source.—The oil distilled from the dried heartwood of *Santalum album*. Contains not less than 2 p.c. w/w of esters calculated as santalyl acetate, and not less than 90 p.c. w/w of free alcohols, calculated as santalol.

Characters.—Pale yellow or nearly colourless, viscid, oily liquid; odour, strongly aromatic; taste, unpleasant. Sp. gr. 0.973 to 0.985.

Composition.—The chief constituent is (1) *Santalol*, a mixture of two sesquiterpene alcohols. (2) An aldehyde, *santalal*. (3) Esters, free acids, etc.

B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

Non-official Preparation

1. **Liquor Santali Co., B.P.C.**—Ol. Santali 5, Sp. Cinnamom 0.25, Tr. Buchu 17, Tr. Cubebs 15, Alcohol *q.s.* to 100. *Dose.*—1 to 2 drs. or 4 to 8 mils.

Pharmacology and Therapeutics

Externally.—Sandal-wood oil is used in perfumery. In India it is sometimes applied to scabies with good effects.

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Internally.—Its action closely resembles copaiba. It is eliminated by the genito-urinary and bronchial mucous membranes, which it stimulates and disinfects, especially the former. Posner thinks that it has a specific action on the prostatic portion of the urethra. It is used with great benefit in 15 to 20 m. doses three times a day in **acute** and **chronic gonorrhœa.** When there is much burning, it is a good plan to give small doses (5 to 10 ms.) every hour, to prevent the urine from irritating the mucous membrane. Being more pleasant, it can be given as a substitute for copaiba, but the combination of the two gives better results. It must be continued for two weeks, to prevent a recurrence, after the discharge has stopped. It has also been found serviceable in chronic fetid bronchitis and cystitis in 10 m. doses.

BUCHU

Buchu

Syn.—Buchu Folia; Bucco; Diosma.

Source.—The dried leaves of *Barosma betulina.*

Characters.—From 12 to 20 mm. long, bright green or yellowish-green, rhomboid-obovate, glabrous, somewhat warty, margin denticulate, apex blunt, recurved, with visible oil glands. Odour and taste, strong and characteristic.

Composition.—(1) A *volatile oil* (1.3 to 2 p.c.) containing *diosphenol*, which forms crystalline deposits on exposure. (2) *d*-limonene, dipentene and menthone, *mucilage* and diosmin.

B.P. Dose.—15 to 30 grs. or 1 to 2 grm.

Official Preparations

1. **Infusum Buchu Concentratum.**—40 p.c. **B.P. Dose.—60 to 120 ms. or 4 to 8 mils.**
2. **Infusum Buchu Recens.**—5 p.c. **B.P. Dose.—1 to 2 oz. or 30 to 60 mils.**

Pharmacology and Therapeutics

Internally.—The action of buchu is due to the volatile oil which it contains, and it is a **diuretic** and **mild urinary antiseptic.** In medicinal doses it causes a sensation of warmth in the stomach, and in large doses nausea and vomiting. The volatile oil is readily absorbed into the blood and is mostly excreted by the kidneys which it stimulates, and partly by the bronchial mucous membrane which is also gently stimulated. During its elimination it soothes and disinfects the urinary passages and imparts a peculiar odour to the urine. It is chiefly used to allay the irritability of the urinary tract, especially the bladder, and is therefore very serviceable in cystitis, irritability of the bladder, urethritis, gonorrhœa, pyelitis, etc. If continued too long in large doses it may harm the kidneys. It is largely used as fresh infusion which forms a good vehicle for mixtures.

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GROUP XIV

DRUGS ACTING ON THE GENITAL ORGANS

Uterus.—The action of drugs on the uterus is difficult to analyse. Experiments made with isolated organs or on intact animals show that the movements are irregular and differ in different animals. The virgin, the pregnant and the non-pregnant uteri also show different types of activity. The movements are myogenic and although not affected by the section of the uterine nerves yet the activity is regulated by the extrinsic nerves. A characteristic feature of the uterine muscle is that it is subject to cyclical changes which occur during menstruation and more specially during pregnancy.

The uterus is supplied by the sympathetic through the hypogastric which contains both the excitor and inhibitor nerves. Stimulation of the sympathetic therefore is followed by a mixed effect, and the contraction or relaxation depends upon the relative preponderance of the two sets of fibres, but this varies in different species of animals and even in the same species, whether virgin or pregnant (*see* adrenaline, page 280). The parasympathetic supply is rather feeble and uncertain and is not generally recognised.

The study of the uterine movements can be made either in the intact animal or in the isolated organ. The movements of the human uterus can be observed with X-rays after filling the cavity with lipiodol.

The pregnant uterus is more sensitive to the effect of drugs than the virgin or non-pregnant one. During pregnancy the uterus undergoes spontaneous contraction which becomes stronger towards the latter part of pregnancy.

The function of the female sex organs is controlled and regulated by a complicated arrangement of the different endocrine glands. The ovaries show cyclic activity which is supposed to be regulated by the anterior pituitary and the phenomena of menstruation depend upon the activity of the ovaries and their removal is followed by stoppage of mentsruation (artificial menopause) with atrophy of the uterus. In congenital absence of the ovaries, or when they are rudimentary, a condition similar to amenorrhœa follows. The luteal hormone, *progestin*, is of great value for the maintenance of pregnancy, and implantation of ovum cannot occur in the absence of the corpus luteum which enlarges during pregnancy, and it has been suggested that its hormone has an inhibitory effect on uterine contraction while its removal in early pregnancy is followed by abortion. Towards the end of pregnancy it degenerates and the uterus becomes hypersensitive and reacts to an increased secretion of oxytocin from the pituitary resulting in termination of pregnancy.

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Ecobolics or oxytocics are drugs which cause expulsion of the contents of the uterus by contracting the uterine muscle. They may be *direct* or *indirect.*

Direct ecbolics act by stimulating the uterus to contraction. They are, histamine, pituitary, quinine, barium and lead which act by stimulating the muscle directly; tyramine, ergotoxine, physostigmine and pilocarpine act by stimulating the endings of the nerves supplying the uterus; and strychnine which stimulates the centre. Hydrastis probably acts in the same way as ergot or pituitary. Of these, pituitary extract, ergot and histamine are most powerful and reliable. Lead is often used as an abortifacient for criminal purposes.

Indirect ecbolics act by producing congestion of the pelvic viscera. They are drastic purgatives and aloes; irritating oils like savine and pennyroyal; irritants like cantharidin, etc.

Emmenagogues are drugs which increase or restore menstrual flow when deficient or absent. They cause congestion of the pelvic viscera. Most ecbolics when used in small doses to non-pregnant women act as emmenagogues. Œstrin, the active hormone found in the ovaries and in the urine during pregnancy is chemically related to cholesterol, which when injected produces œstrus in rats. It has been found to give relief in cases of artificial menopause and in regulating menstrual disorders. Heat or counter-irritants applied over pelvic regions, *e.g.*, hot hip bath, hot mustard bath or mustard poultice help the onset of menstruation. Amenorrhœa is common in women suffering from anæmia, chronic malaria, cachexia and in general rundown conditions, when appropriate treatment with iron, quinine, codliver oil or other tonics are helpful.

Mammary Glands.—These glands are intimately related to the sex glands, and their development is arrested after extirpation of the ovaries, while their growth continues in the normal way after successful transplantation in young animals. Just as the development of the glands is regulated by the internal secretion of the ovaries, corpus luteum and the placenta, so also the secretion of milk is regulated by hormones. Drugs which increase the secretion of milk are called **galactogogues.** An injection of placental extract increases the secretion of milk; so does pituitary extract. The secretion of milk is also influenced by various other factors and reflexes. It is possible that the nerve supply of the mammary glands is different from other glands. Thus pilocarpine, which increases the secretion of other glands, has no effect on the secretion of milk. Urea is supposed to be a true galactogogue.

Antigalactogogues are drugs which diminish the secretion of milk; as iodides.

Several drugs are excreted by the milk and in doing so

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alter its composition. Thus rhubarb, senna, jalap, scammony and castor oil may produce looseness in suckling babies, when given to their mothers. Iodides, bromides, arsenic, mercury have been demonstrated in the milk when given to women. Copaiba, asafetida, oil of turpentine impart a disagreeable odour to the milk. Opium given to nursing mothers may cause symptoms of poisoning to infants.

Aphrodisiacs.—These are drugs which cause sexual excitement and increase sexual power. The centre lies in the lower part of the spinal cord, and excitement can be produced purely reflexly by sensory stimuli from various parts such as the nose, eye, ear, mamma, etc. It is probable that the centre for erection is affected reflexly by the fullness of the bladder and of the seminal vesicles. The centres are also controlled by internal secretions. Steinach has shown that the embracing reflex, which disappears after castration, reappears after injection of testicular substance. This he attributes to the internal secretion of the interstitial tissue and not to that producing spermatozoa. The internal secretions of thyroid and of the hypophysis play important part in the development of the genital organs. Aphrodisiacs are :—Strychnine, damiana, yohimbine, etc.

Anaphrodisiacs are drugs which diminish sexual passion and power. These are iodides, bromides, belladonna, etc.

Class A : Ecbolics

Ergot, Hydrastis, Pituitary Extract

ERGOTA

Ergot

Syn.—Secale Cornutum ; Ergot of Rye.

Source.—The sclerotium (mycelium or spawn) of *Claviceps purpurea* originating in the ovary of *Secale cereale*, the common rye. Ergot is the diseased rye filled with the mycelium of a small fungus. Contains not less than 0.05 p.c. of the total alkaloids of ergot, calculated as *ergotoxine*.

Characters.—1.5 to 4 cm. long and 2 to 7 mm. broad, fusiform, obscurely 3 or 4 sided, straight or arcuate ; longitudinally furrowed and transversely cracked ; brittle ; dark violet-black ; whitish or pinkish white internally, showing darker lines radiating from the centre. Odour and taste, characteristic.

Composition.—By the growth of the fungus the proteins of the rye are broken down and various amino-acid derivatives are formed, to which ergot owes its properties. The chief constituents are : (1) The following alkaloids : (*a*) *Ergotoxine* $C_{35}H_{41}N_5O_6$ an amorphous alkaloid soluble in alcohol, but insoluble in water ; sphacelinic acid is an impure specimen of this alkaloid and ergotinine an inert crystalline base. *Ergotamine* resembles ergotoxine if not actually identical. (*b*) *Sensibamine*, and (*c*) *Ergoclavine*. Recently another alkaloid, viz. (*d*) *Ergometrine* has been isolated by Dudley and Moir who gave the formula, $C_{19}H_{23}O_2N_3$. *Ergotocine*, *Ergostetrine* and *Ergobasine* are possibly identical with ergometrine. (2) *Tyramine* or para-hydroxyphenyl-ethylamine. It resembles adrenaline in action. Derived from

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amino-acids during putrefaction of organic matter by the elimination of CO_2. (3) *Ergamine* or *Histamine* obtained from histidine through the agency of putrefactive organisms just as tyramine is obtained from tyrosine. (4) *Agmatine*, an amino-acid derivative, resembles ergamine, but weaker. It also contains fixed oil 30 p.c., tannin, and some colouring matter.

Official Preparation

1. **Extractum Ergotæ Liquidum.**—Contains 0.06 p.c. w/v of the total alkaloids of ergot, calculated as ergotoxine. After storage contains less than 0.04 p.c. w/v of ergotoxine, or $\frac{1}{90}$ gr. in 20 ms. **B.P. Dose.—10 to 20 ms. or 0·6 to 1.2 mils.**

ERGOTA PRAEPARATA

Prepared Ergot

Source.—It is ergot powdered and immediately deprived of its fat. Contains 0.1 p.c. of the total alkaloids of ergot, calculated as ergotoxine, or $\frac{1}{60}$ gr. of ergotoxine in 15 grs.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

ERGOTOXINAE AETHANOSULPHONAS

Ergotoxine Ethanesulphonate

Source.—Is the ethanesulphonate of an alkaloid, ergotoxine, obtained from ergot. Contains 83.6 p.c. ergotoxine.

Characters.—Colourless, acicular crystals; odourless. Sparingly *soluble* in water, more in alcohol (90 p.c.), easily in methyl alcohol.

B.P. Dose.—$\frac{1}{120}$ to $\frac{1}{90}$ gr. or **0.0005 to 0.001 grm.** subcutaneously or intramuscularly.

Pharmacology

Ergotoxine.—($\frac{1}{100}$ to $\frac{1}{50}$ gr.). The exact site of action of this alkaloid has not been definitely established. It has the following effects, viz. (*a*) stimulates and subsequently depresses the sympathetic nerve-endings, but only when they are motor; (*b*) stimulates the involuntary muscles directly and renders tissues insensitive to adrenaline. It therefore antagonises the motor effects of adrenaline upon the plain muscles. It increases the tone of almost all the plain muscles throughout the body, but the action on the arteries is most marked, which become constricted with stasis of peripheral circulation. Subsequently there is thickening of the vessel walls and the small vessels contain hyaline plugs. Small doses injected intravenously stimulate the vessels supplied with vaso-constrictor nerves and cause a rise of blood-pressure with slowing of the heart. A second injection causes a smaller rise or no rise at all due to paralysis of the motor nerve-endings of the sympathetic. An injection of adrenaline at this stage causes the arteries to dilate, the so-called "vaso-motor reversal of Dale." In small doses it stimulates and in large doses depresses the myo-neural junction of the vaso-constrictor nerves, but leaves the

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dilators active. As it has no effect on the inhibitory sympathetic endings it has no effect on the contracted bronchioles nor on the stomach or intestinal movements. By stimulating the motor sympathetic endings it increases the tone and rhythmic contraction of the uterus. It has no effect in constricting the vessels when locally applied, and since its absorption is not retarded from the stomach like adrenaline all these effects are elicited when given by the mouth.

Tyramine ($\frac{1}{2}$-1 gr.) acts like adrenaline, but the effects are not so prompt or powerful but are of longer duration. These effects are observed even when it is given by the mouth or injected subcutaneously. It contracts the bronchial muscles and therefore does not relieve asthmatic attacks. It causes marked contraction of the uterus specially when pregnant.

Histamine or **Ergamine.**—Histamine occurs in extracts of all vegetable and animal tissues and is formed by the breakdown of proteins in the intestine by the bacterial action. Administered by the mouth it is destroyed by the digestive juices, therefore very little effect is observed when given by this route. Injected intravenously or subcutaneously it contracts all plain muscles including the uterus, bronchial and the intestinal muscles in the same way as pituitary extract. The action on the uterus differs from the other two in that it contracts both the gravid and non-gravid uterus. Although the muscles of the arteries are contracted, it dilates the capillaries and causes a fall of blood-pressure like peptone or anaphylactic shock. As mentioned elsewhere (*see* page 276) the absorption of histamine or some amine from the damaged tissue is the cause of shock either surgical or from extensive burns. Its effects on circulation are complex. In certain species of animals, *e.g.*, rabbits and guinea-pigs, it causes a rise of blood-pressure, but in most animals there is a fall. It increases the gastric secretion, specially the acid component, and has been used intramuscularly to test the secretory response of the stomach in gastric disorders (*see* page 316). While the action of ergotoxine is slow and prolonged that of amines is prompt and fleeting.

Recently ionization of histamine has been used with good results in the treatment of fibrositis and neuritis and in chronic rheumatic affections.

Internally. **Gastro-intestinal tract.**—Ergot has a disagreeable bitter taste and increases salivary secretion. Since the sympathetic supply to the intestine is inhibitory, ergot has very little effect on the movements of the intestine.

Heart and circulation.—Ergot has decided influence on the heart, which beats more vigorously, the systole is more complete and the output is much greater. This effect is due partly to tyramime exciting the sympathetic nerve-endings like adrenaline and partly to ergamine acting on the cardiac

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muscle. The rate is slowed from increased blood-pressure stimulating the vagal centre and by the direct action on the muscle.

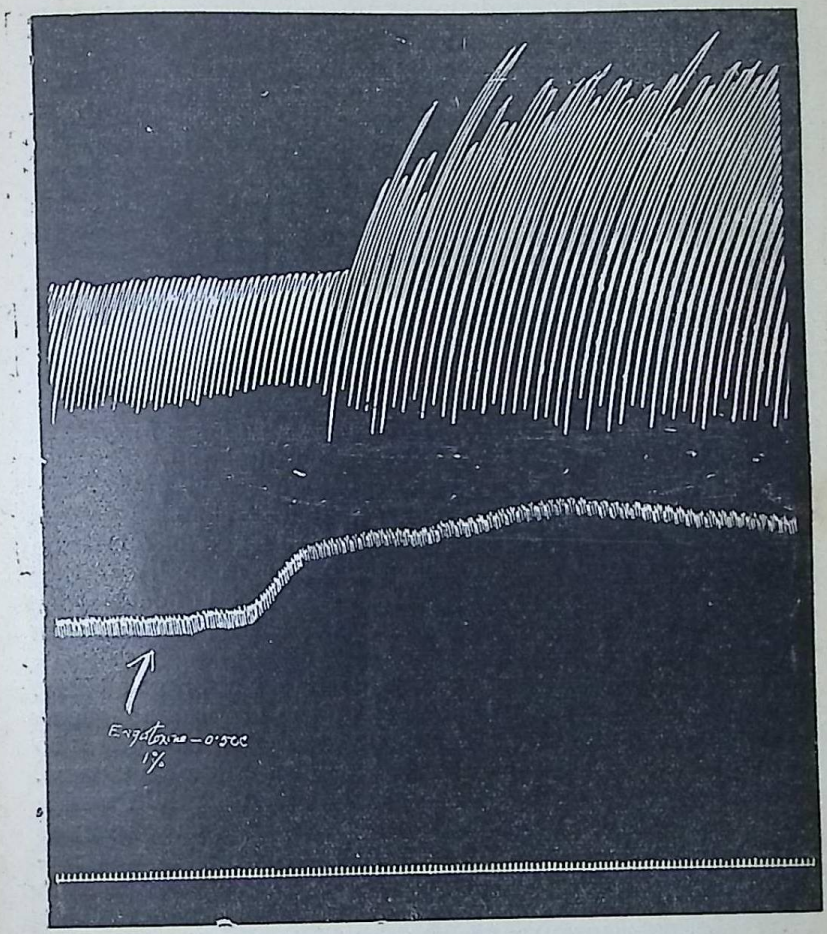

Fig. 9.—Dog. Respiration and Blood-pressure.
At point of arrow 0.5 c.c. of 1 p.c. solution of ergotoxine was introduced into the femoral vein. Note stimulation of respiration and rise of blood-pressure. After a large dose the respiration is depressed making it slower and weaker.

The effect on blood-pressure is variable, no change being observed unless given intravenously; this is possibly due to the complex action of its different constituents. It causes **profound rise of pressure** from the powerful contraction of the arterioles all over the body. This effect is partly due to ergotoxine and partly to tyramine on the peripheral vessels causing constriction of the vessels of the abdomen and the extremities by stimulating the nerve terminations in the

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vessel walls much in the same way as adrenaline. Sometimes when given intravenously there may be a fall of pressure or an initial fall followed by a rise due to the presence in large amounts of histamine or even choline. It should be remembered, however, that the pulmonary pressure rises from increased output of the right heart. In fact it has no effect on pulmonary vessels. Prolonged constriction of the vessels caused by ergot, if continued long, may cause gangrene in different parts of the body leading to "gangrenous ergotism." Toxic doses paralyse the vaso-motor centres and the cardiac muscle, producing a fall of blood-pressure.

Uterus.—Ergot powerfully contracts the impregnated uterus of women and lower animals, specially when in labour, thereby expelling its contents. Hence it is a powerful ecbolic. This action is elicited within twenty minutes after administration of the liquid extract by the mouth, and is due to ergotoxine. It is doubtful if ergamine has any share in this effect inasmuch as it would not produce any marked effect when given by the mouth. The contractions become more frequent than the normal ones and also more prolonged and irregular. In large doses given as injection, it causes tetanic spasms, *i.e.*, the uterus may contract very powerfully and may remain in that state for a longer time. In doses given to produce uterine action, ergot has no effect either on the blood-pressure or on the alimentary canal. Owing to the presence of ergamine it has a pronounced effect on the non-gravid uterus, so that it augments menstruation and acts as an **emmenagogue.**

Moir * pointed out that the liquid extract of ergot of B.P. 1914, which contained no alkaloid of the ergotoxine group produced uterine contraction and he attributed this effect to the presence of an oxytocic principle of an unknown nature. Subsequently Dudley and Moir † isolated an alkaloid which they named *ergometrine*, and they believe that the presence of this alkaloid in the liquid extract of B. P. 1914 was responsible for the oxytocic effect. The action of ergometrine differs from that of the alkaloids of the ergotoxine group in that the effects are produced within 5 to 8 minutes given by the mouth, 3 to $4\frac{1}{2}$ minutes when given intramuscularly, and within a minute when given intravenously. Moreover when used for a prolonged period it has no gangrene producing properties, and its use is not followed by depression, headache and nausea so common with ergotoxine, ergotamine and ergoclavine. For clinical use the dose of ergometrine is 0.5 to 1 mg. by mouth; 0.5 mg. for intramuscular injection; and 0.125 mg. for intravenous use.

* *British Medical Journal, June 18,* 1932.
† *British Medical Journal, March* 16, 1935.

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Respiration.—After an intravenous injection of ergotoxine the respiration is increased both in force and frequency, possibly due to stimulation of the centre. Large doses depress the centre when the respiration becomes slow and weak. Death occurs from asphyxia caused by the spasm of the muscles and weakness of the respiratory centre.

Eye.—After a momentary dilatation ergot powerfully contracts the pupil when injected intravenously. This effect is due to the direct action of ergotoxine on the iris, and is not counteracted by atropine.

Nervous system.—It has little effect on the brain. The highest centres are not affected by medicinal doses, nor even by a single large dose. It produces changes of a sclerotic nature especially in the postero-external columns of the cord, and induces, when it is given for a long time, a train of symptoms known as "spasmodic ergotism."

Secretion.—The secretion of saliva, sweat, milk and urine is diminished probably from the disturbance of the local blood-supply to the glands by the general vascular contraction.

Acute toxic action.—Acute poisoning is rare but sometimes large doses are taken to procure abortion. The symptoms are weak, rapid pulse, tingling and itching of the skin, excessive thirst, gastro-intestinal irritation, uterine hæmorrhage followed by abortion. Unconsciousness and collapse. Abortion usually follows, but sometimes even in fatal cases there is no abortion.

Chronic toxic action or Ergotism.—Poisoning by ergot rarely occurs when used medicinally, but it is very frequently seen amongst the poor who live on diseased rye. It then shows itself under one or other of the two forms described below.

1. **Gangrenous Ergotism.**—Various parts of the body, especially the extremities, suffer from imperfect blood-supply, owing to the contraction and thickening of the walls of the blood-vessels, thereby leading to a process of gangrene. It should not be mistaken for **pellagra**, a disease characterised by indolent ulcers on the skin, or for **Raynaud's Disease.**

2. **Spasmodic Ergotism.**—In this variety, the patient first feels a sensation of itching, or tingling, and of insects crawling over the body, followed by a sensation of numbness and of local anæsthesia. These symptoms appear first in the hands and face, then spread over the body. The sensory impairment is soon followed by signs of motor irritation such as tonic contraction of the muscles, especially of the extremities; and later on by the development of a staggering gait. Vomiting and diarrhœa often accompany this variety, and dimness of sight, loss of hearing, and epileptiform convulsions are occasionally present.

It should not be confounded with *lathyrism*, palsy of the lower extremities caused by the use of chick-pea (*Lathyrus sativus* and *Lathyrus cicera*) as the only article of food.

Therapeutics

The chief use of ergot is in obstetric practice to increase uterine contraction. One school advocates its use in all cases with weak contraction as an ecbolic, while others recommend its use only after the explusion of the child, and will

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not use during labour, even at the late stage for fear of prolonging labour or even causing death of the child from asphyxia. In any case the use of ergot as an ecbolic should be restricted only to those *cases of uterine inertia in which there is no mechanical obstruction to the passage of the child*; otherwise the child's life may be endangered by the prolonged tonic contraction of the uterus, or if the resistance is too great it may cause rupture of the organ. If however it is used at all the dose should be small and well-regulated so that there cannot be any possibility of the tonic contraction. Ergot therefore is not used as a rule till after the expulsion of the placenta, when it ensures firm contraction of the uterus and prevents post-partum hæmorrhage. In multiparas who are often subject to this sort of bleeding, it is a wise plan to administer ergot just after the expulsion of the fœtus, or even before its birth if there be no contra-indication to its administration. In urgent cases it is better to give an injection of pituitary extract along with a dose of ergot by the mouth so that the action of ergot will be manifest by the time the effect of pituitary passes off. It is often given combined with quinine during the puerperium to help involution of the uterus. The following is a good post-partum mixture, *viz.*, Ext. ergot. liq. 30 ms., quinine hydrochlor. 4 gr., spt. chloroformi 15 ms., tr. digitalis 5 ms., aqua ad. oz. 1.

As a *hæmostatic* it has entirely lost its reputation; for it is difficult to understand how a drug which causes general constriction of the vessels could stop internal hæmorrhage, as this constriction is attended with general rise of blood-pressure. But its effect in stopping post-partum hæmorrhage is due to a different factor and is the result of obliteration of the open sinuses by the sustained contraction of the uterus. Its use therefore in any form of internal hæmorrhage other than uterine is irrational. As it increases pulmonary pressure it should not be used in hæmoptysis.

Ergot has been used in many other forms of bleeding from the uterus and sometimes with good results. For instance it is used in menorrhagia, metrorrhagia and in bleeding from various forms of uterine fibroids.

HYDRASTIS RHIZOMA

Hydrastis. (Not official)

Syn.—Golden Seal.

Source.—The dried rhizome and roots of *Hydrastis canadensis.*

Composition.—It contains alkaloids (1) *Berberine*, 1.5 to 4 p.c. (2) *Hydrastine*. 2.5 p.c. and (3) *Canadine.*

Non-official Preparations

1. **Extractum Hydrastis Liquidum.**—2 p.c. hydrastine. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.

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2. **Tinctura Hydrastis.**—Liquid extract 1, alcohol (60 p.c.) 10. *Dose.*—½ to 1 dr. or 2 to 4 mils.

3. **Hydrastina.** *Syn.—Hydrastine.*—A white crystalline alkaloid. Acts like quinine, though milder. *Dose.*—¼ to 1 gr. or 0.015 to 0.06 G.

4. **Hydrastinæ Hydrochloridum.**—A white or creamy white powder. Odourless and soluble in water. *Dose.*—0.01 grm. or ¼ gr.

5. **Hydrastininæ Hydrochloridum.**—A pale yellow crystalline powder, soluble in water. *Dose.*—¼ to 1 gr. or 0.015 to 0.06 G.

Pharmacology

Externally.—Hydrastis acts as a **stimulant and antiseptic** to ulcerated surfaces.

Internally.—Being bitter, it promotes appetite and digestion, and stimulates gastric and intestinal secretion and peristalsis. It is therefore a **stomachic tonic** and **laxative.** It contracts the unstriped muscular fibres of the arteries and those of the uterus, hence it is a **hæmostatic** and **ecbolic,** though the contractions are not so strong as those produced by ergot. The action is direct on the uterine muscle, although there is some stimulation of the hypogastric ganglia which is of minor importance. Hydrastine is a mild **febrifuge.** On the nervous system its action resembles strychnine, and it increases the reflex excitability and slightly stimulates the vagus, vaso-constrictor and respiratory centres. In large doses it causes convulsions. On the circulation its effects are too uncertain to be of any use therapeutically.

Therapeutics

Externally.—Hydrastis has been employed as a dressing to chronic unhealthy ulcers, and as an application to eczema (5 to 20 grs. in lard 1 oz.). The tincture or the liquid extract (2 or 4 drs. to 1 pint) makes an efficient lotion for injection in **gonorrhœa** after the acute stage, gleet, leucorrhœa, cystitis, otorrhœa, etc.

Internally.—Hydrastis is one of the most useful remedies we have for chronic **gastric** and **intestinal catarrh,** especially of chronic alcoholism. It has been largely employed in arresting **hæmorrhages,** especially **uterine.** In short, it may be used in all cases where ergot is indicated. It is however a *weak substitute for ergot* and cannot replace either ergot or pituitary in the treatment of post-partum hæmorrhage. As an antiperiodic it is far inferior to quinine.

EXTRACTUM PITUITARII LIQUIDUM

Pituitary (Posterior Lobe) Extract

Syn.—Liquor Pituitarii; Solution of Pituitary Extract.

Source.—An aqueous extract of the posterior lobes of pituitary bodies of oxen or other mammals. Contains 10 units per millilitre.

Characters.—A clear, colourless liquid with a faint odour. *Reaction,* between the limits corresponding to the values *p*H 3 and *p*H 4.

Composition.—(1) *Oxytocin* or *pitocin,* oxytocic principle, causes contraction of the uterus and without any effect on blood-pressure. (2) *Vaso-pressin, or pitressin,* causes rise of blood-pressure and vaso-constriction. Causes both diuresis and anti-diuresis, and relieves post-operative intestinal stasis.

B.P. Dose.—2 to 5 units (0.2 to 0.5 mils) subcutaneously.

Pharmacology

Heart and blood-vessels.—After an intravenous injection of the extract there is a rise of **blood-pressure.** A second

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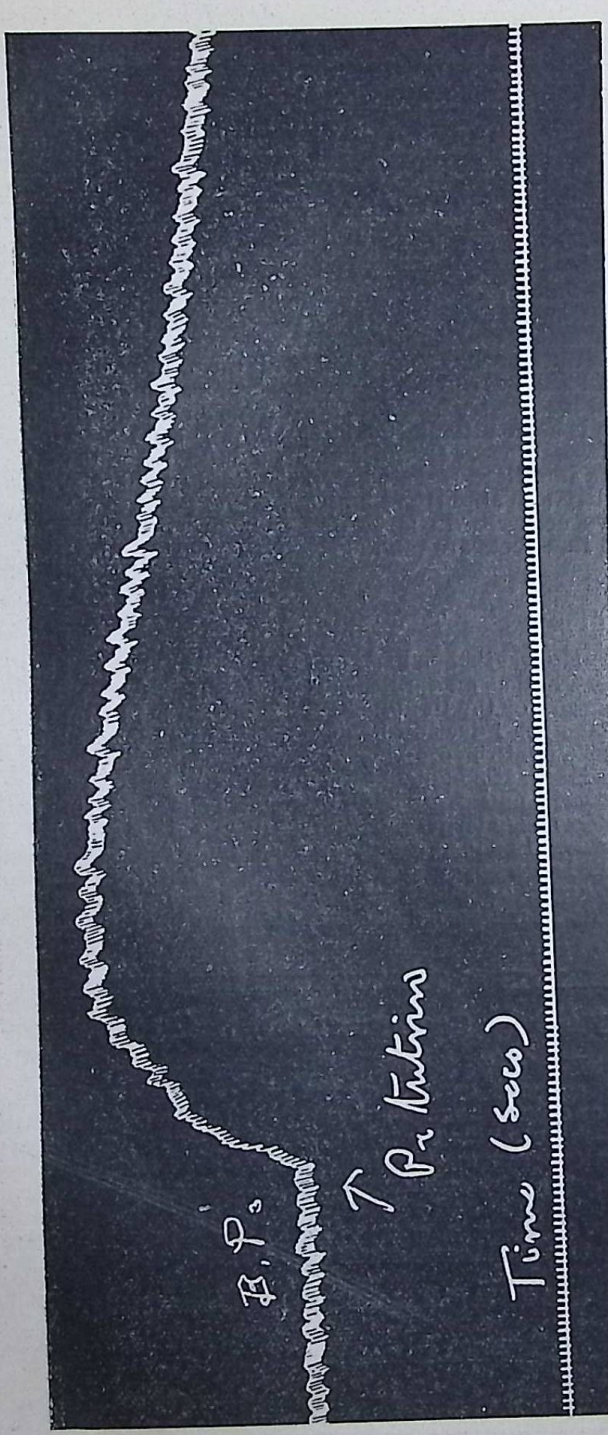

Fig. 10.—Showing the prolonged effect of Pituitrin on Blood-pressure. Compare the effect of Adrenaline (page 278), and Ephedrine (page 283)

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injection often has no effect if given shortly after the pressure has returned to its normal height. The effect, although not so sudden as adrenaline, is more prolonged and lasting; but there is a marked difference in the site of action and the effect is due to the stimulation of the muscles of the arteries and not the myoneural junction of the vaso-constrictors. The arterial pressure begins to rise within a minute and may last for about half an hour. Dale has shown that there is an enormous difference in the strength of different preparations, and in many instances it causes a fall in pressure, a purely histamine-like effect. This is not due to the essential principle but to the presence of some impurity causing depression of the heart. It also constricts the coronary, pulmonary and cerebral arteries. Removal of the gland causes loss of tonus of the capillaries of the frog which is restored by the administration of the extract. It is possible that the pituitary secretes a substance which maintains the normal tone of the capillaries and that substance is vasopressin.

It **slows the heart** due partly to stimulation of the vagus centre from increased blood-pressure and partly from its direct action on the cardiac muscle. The rate is quickened during the fall of pressure. Whether the rate is slowed or quickened the output of the heart is diminished and the **pulmonary pressure falls.** In intact animals the heart muscle is weakened from diminished oxygen supply from coronary constriction.

Absorption.—It is not absorbed by the unbroken skin and administered by the mouth it is destroyed by the digestive juices. Given per rectum or applied to the nasal mucosa it is sufficiently absorbed to elicit antidiuretic effect and contraction of the uterus. Full therapeutic effects are elicited when given subcutaneously or intramuscularly. The pressor effect is well marked after intravenous use.

Alimentary canal.—It decreases salivary, gastric, pancreatic and intestinal secretions. Both subcutaneous and intravenous doses have a marked effect on the intestinal muscles causing increased tone and peristalsis. This effect is antagonised by atropine. Quigley and Barnes have however shown that the gastro-intestinal movements are depressed by both the active principles in intact animals. The effect on excised strips of intestine is that of stimulation, though variable and complex.

Kidneys.—Its use is followed by **diuresis** which is the result of improved renal circulation and high blood-pressure. But this is followed by **diminished secretion** which is of longer duration. In man and in unanæsthetised animals it diminishes the secretion specially when polyuria is present, as in cases of diabetes insipidus. This effect has been differently explained by different observers. Sollmann attributes

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it to a specific limitation of the water-excreting capacity of the kidneys, while others hold that this is due to the existence of a special centre in the brain which regulates the water exchange of the body and which can transfer water from the tissues to the blood, thus exciting diuresis. Pituitary is supposed to regulate the function of this centre. Richards has pointed out that the antidiuretic effect is helped by the contraction of the glomerular capillaries. There can be no doubt that the general contraction of the vessels which is also shared by the glomerular capillaries contributes to the antidiuretic effect as this lessens the filtration surface. It is antagonistic to insulin, as direct stimulation of the gland or injection of the extract is followed by hyperglycæmia and glycosuria (Dale and Burn). This antagonism is not a direct chemical one but is performed through the intermediary of the liver. The vasopressin moiety empties the glycogen reservoirs in the liver, while insulin stores up dextrose as glycogen. It increases the excretion of chlorides.

Female generative organs.—Pituitary causes powerful contraction of the uterus whether pregnant or not by acting on the uterine muscle. The effect is more rapid (occurring within $2\frac{1}{2}$ minutes) and lasts for a shorter time (less than an hour) than ergot. It differs from adrenaline in that it acts on all animals and has no effect on the nervous mechanism.

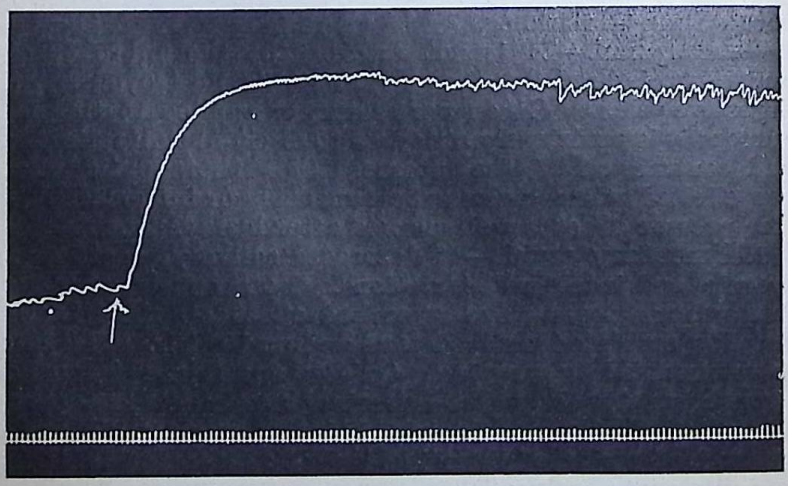

Fig. 11.—Effect of pituitrin on the isolated uterus (non-gravid) of guinea-pig suspended in oxygenated Ringer's solution. Contraction is indicated by the upward movement of the lever.

This action is more marked than its effect on the intestine and is elicited whether the drug is given hypodermically or intravenously. It increases the secretion of milk and is a galactogogue. It does not actually increase the amount of

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milk secreted, but only helps the expulsion from increased contraction of the milk glands.

Respiration.—Respiration is first strengthened and then becomes shallow and slow. After repeated injections no effect is produced. Sometimes bronchial muscles are contracted due to the presence of histamine as an impurity. Pure preparations have no such effect.

The actions of pituitrin and adrenaline are compared in the following table :—

Pituitrin	Adrenaline
1. Causes rise of blood-pressure, action not so rapid and the effects last longer.	Causes rise of blood-pressure, action more rapid, and the effects of shorter duration.
2. Slows and weakens the heart.	Accelerates the heart.
3. Constricts the coronary and pulmonary vessels.	Dilates coronary vessels.
4. Acts as a diuretic from passive dilatation of the renal vessels followed by oliguria.	Constricts renal arteries.
5. Stimulates the intestine, bladder and pregnant uterus.	Inhibits.
6. Acts directly on the muscle fibre.	Stimulates the sympathetic nerve-endings.

Therapeutics

For its powerful action on the blood-pressure pituitary extract is largely used in the prevention and treatment of shock, specially occurring during the anæsthesia of severe surgical operations.

The chief use of the drug is in obstetric practice and it is the most valuable means of strengthening weak labour pains and arresting post-partum hæmorrhage. Its use however should be restricted to those cases of uterine inertia where there is no mechanical obstruction to the passage of the child. When used to strengthen labour pains it may, through powerful contraction, actually delay the birth of the child or may cause asphyxia, premature separation of the placenta or even injury to the soft parts.

Because it causes contraction of the intestinal muscles, it is used in tympanites and intestinal paralysis such as those which may occur after surgical operations, or as a complication of some acute infection. It is doubtful whether it does good in all cases, and in advanced cases of intestinal paralysis following an infection, it has often been found to fail. Recently its use has been suggested in gastric ulcer and hyperchlorhydria on the idea that it decreases gastric acidity by increasing the excretion of urinary chlorides, thereby diminishing the chloride content of the blood. Its use has also been suggested in exophthalmic goitre, acromegaly, osteomalacia and gigantism.

As pituitary is an outgrowth of the nasal mucosa, it might

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be absorbed by spraying into the nose, or from plugs of cotton wool soaked in the solution of the extract and inserted high up into the nasal cavity. This method of treatment has been used with success in diabetes insipidus. In fact the administration of the posterior lobe extract diminishes polyuria from any cause. To be effective it should be given either as *intranasal spray* or *hypodermically*.

The whole gland pituitary extract is useful in obesity of pituitary origin which is characterised by deposition of fat around the girdles and commonly occurs in children and adolescents. It is usually given in combination with thyroid extract $\frac{1}{4}$ gr. each and then working up to a point at which the patient loses one to two pounds a week. The writer is not convinced of its value and has failed to reduce any weight when given to carefully selected cases for prolonged periods.

Pituitary (Anterior Lobe) Extract.—It is an active extract of the anterior lobe which when injected will accelerate growth in the young animal or cause the fully grown animal to grow further, will produce precocious sexual development in young female rats, and will bring on menstruation in monkeys. It produces all these effects through the following hormones, *viz.* (1) *growth promoting hormone*, removal of the gland or insufficiency of this hormone is followed by infantilism; (2) *sex hormones*, which consist of *prolan A* and *prolan B*; (3) *thyrotropic hormone*, the loss or insufficiency of this hormone is followed by atrophy of the thyroid with reduction of the basal metabolism, which is prevented by the injection of an extract of the anterior pituitary. Injection of the extract, because of the presence of this hormone, in guinea-pigs produces exophthalmos and hyperthyroidism; (4) *adrenotropic hormone*, removal of the gland leads to atrophy of the adrenal cortex; and (5) *parathyrotropic* hormone; it is possible that osteoporosis and fractures which occur in Cushing's disease are due to an influence radiating from pituitary to the parathyroids. It exhibits two types of cells, *viz.* (1) *chromophobe cells*, without any special affinity for dyes, possibly influence the development of secondary sex characters; (2) *chromophyl cells*, which stain readily and have been subdivided according to the character of the granules into *eosinophyl cells* and *basophyl cells*, the former yeilds the growth-promoting hormone and the latter helps in the production of sex hormones.

Zondek and Aschheim have shown that the prolans are present in the urine of pregnant women from a very early stage and are as a rule absent from the urine of non-pregnants and males. They have further shown that implantation of the anterior pituitary into immature female rats induces sex maturity, *i.e.* precocious ovarian activity, and the same results are obtained by injecting the blood or urine of pregnant women.

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The injection of *prolan A* or an acid extract of anterior pituitary stimulates the ovarian follicles and helps them to ripen and ovulate with liberation of œstrin which sets up the proliferative changes in the uterine mucosa; while injection of *prolan B* or an alkaline extract of anterior pituitary produces luteinization of the follicular walls with rapid formation of corpora lutea and fixation of the ova, inhibition of ovulation in mature chickens, hypertrophy of the uterus and increased lactation. If the urine of pregnant women, which contains the œstrogenic hormone, is injected several times daily for three days into immature rats or mice, it produces hyperplasia of the genital tract and the mammæ. This has been used for diagnosis of pregnancy and is known as Zondek and Aschheim test and can be obtained when pregnancy has only lasted for less than a month and remains positive till twelve days after delivery.

Therapeutic Uses.—It is supposed to act as a specific in adiposogenital dystrophy, a disease characterised by retarded sexual development, adiposity, lethargy and deficient vital functions. It is also of value in atrophy of the anterior lobe. Dried gland has been used by the mouth and also an extract hypodermically, but it is doubtful if when given by the mouth it produces any marked improvement.

The sex hormones are sold under the name of *Antuitrin*, which in relatively small doses has been used in sexual infantilism with amenorrhœa and delayed puberty, functional sterility and dysmenorrhœa and delayed menstruation due to deficiency of the hormone of the corpus luteum. In larger doses it has been used in menorrhagia and metrorrhagia and in the treatment of climacteric hæmorrhage and threatened abortion. The usual dose is 1 c.c. hypodermically. or 1 gr. of the anterior lobe by the mouth.

Antuitrin is prepared from the urine of pregnant women and contains both prolan A and prolan B. The potency of the solution is judged by the amount necessary to cause the formation of corpora lutea when injected into immature female rats (1 c.c. contains 100 rat units). *Dose.*—1 to 2 c. c. hypodermically for 10 to 12 daily injections.

Sex Glands

The Ovary.—The ovary performs several diverse functions. It is responsible for the development of the secondary sexual characters of women. Menstruation depends upon their proper functioning, while their removal is accompanied by stoppage of menstruation. In animals the phenomena of 'heat' or *œstrus* do not occur in the absence of ovary. It also helps to fix the embryo into the uterus until it is sufficiently developed to survive birth and to maintain an independent existence. Three different hormones have been isolated from the ovary, *viz.* (*a*) *œstrin* (*theelin* or *folliculin*); (*b*) *corpus luteum hormone* or *progestin*, concerned in the prevention of ovulation and is largely antagonistic to œstrin; and (*c*) *interstitial hormone*, causes secretion of posterior pituitary lobe.

1. **Œstrin.**—It is a term applied to hormones present in the ovaries, placenta, fœtal membranes and liquor amnii, and the urine

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of pregnant women. It can also be obtained from the *testes* and other tissues of the male. It has been isolated in pure crystalline form.

The unit is defined as the specific œstrus-producing activity in 0.0001 mgrm. of the standard preparation which is a hydroxyketonic form of the hormone obtained from urine of pregnancy, and kept at the National Institute of Medical Research, London. The œstrus-producing activity is the power of producing in adult female rats or mice, completely deprived of their ovaries, the cellular changes in the vaginal secretion characteristic of normal œstrus.

When subcutaneously injected into spayed rats, it produces typical œstrus, promotes the growth of uterus and vagina in the immature, causes hyperplasia of the endometrium in the mature, and during labour may sensitise the uterine muscle to the expulsive action of the posterior pituitary. In other words it produces all those changes which facilitate the fertilisation of an ovum.

Since natural or artificial menopause is often accompanied by a variety of nervous symptoms, ovarian extract (which contains œstrin), or œstrin may be administered in those conditions depending on disordered uterine or ovarian functions, menstrual irregularity and other nervous disturbances occurring during menopause, or following artificial removal of ovaries. It has also been used in hyperemesis gravidarum, sexual frigidity and in hypofunctions of the ovaries, e.g. amenorrhœa, functional sterility and genital hypoplasia.

It may be administered in the form of desiccated ovary in doses of 1 to 10 grs. by the mouth; or as œstrin or theelin by hypodermic or intramuscular injection, daily or on alternate days, for six to eight injections. Since it is said to be absorbed from the vaginal mucous membrane it is used in the form of pessaries.

Theelin.—It is ketohydroxy-œstrin. 1 grm. represents 3,000,000 rat units. Used as injection or as pessary. *Dose.*—50 units a week increased to 4 to 6 daily injections of 50 to 100 units. 1 c.c.=50 units.

Theelol is effective when given by the mouth. It is trihydroxyœstrin. *Dose.*—1 to 3 capsules daily or 50 to 150 rat units.

2. **Corpus Luteum.**—Its hormone *progestin*, or an extract of corpus luteum administered to virgin animals produces growth of the mammary glands, and it is supposed to control the changes in the uterus which precede the fixation of the ovum, and controls the development of the mammary glands during pregnancy. The gland enlarges during pregnancy and it has been suggested that its hormone (progestin) has an inhibitory effect on the uterine contraction. Its persistence depends on the secretion of anterior pituitary hormone, prolan B, and when this fails towards the end of pregnancy it degenerates making the uterus hypersensitive which reacts to an increased secretion of oxytocin and finally leads to the termination of pregnancy. On the other hand injection of prolan B causes persistence of the corpus luteum and prolongation of pregnancy beyond the normal term.

The action of corpus luteum given by the mouth is uncertain. It has however been used in cases of habitual abortion.

The Mammary Glands.—Mammary substance is related to the uterus and is useful in cases of profuse menstruation of young girls and young women, and the menorrhagia occurring at the time of menopause. It is usually combined with pituitary. *Dose.*—2 to 5 grs. of the desiccated gland, three times a day.

The Prostates.—The frequency of neurasthenic manifestations in persons suffering from prostatic disorders has led to the belief that prostate supplied some element which normally controls the nervous system. With this idea it has been used in the treatment of neuroses that occasionally follow prostatic hypertrophy. There is no reliable evidence that the prostate furnishes an internal secretion. In fact no demonstrable defect has been noticed after removal of the glands.

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Dose.—1½ to 3 grs. two or three times a day.

The Testicles produce an internal secretion which controls the secondary sexual characteristics. The removal of the testes in infants prevents the appearance of the normal changes of puberty. Transplantation of the testes (Voronoff's method) is supposed to cause rejuvenation, and has been tried in the Continent and other places.

Orchidin or *Testiculin* (15 to 30 ms.) hypodermically, or per os has been recommended as an aphrodisiac and for the treatment of various forms of nervous debility, locomotor ataxy and exophthalmic goitre.

Class B : Uterine Sedatives

These are remedies which inhibit uterine contraction, and are therefore of value in the treatment of threatened abortion. They should be avoided during labour as they are liable to cause uterine inertia. Few drugs, however, actually inhibit the uterine contractions, although narcotics and general anæsthetics cause some delay in labour through their effects on the central nervous system. Atropine diminishes uterine contraction by depressing the motor nerve-endings. Apart from these, certain drugs possess the reputation of being uterine sedatives, and are used in *threatened abortion, dysmenorrhœa*, etc. Drugs which relax plain muscles generally also reduce uterine contraction, *e.g.*, nitrites and papaverine. Corpus luteum has the property of reducing the sensitiveness of the uterus to œstrin and also diminishes spontaneous movements during pregnancy. It is therefore sometimes used in cases of threatened abortion.

VIBURNUM

Black Haw. (*Not official*)

Source.—The dried bark of *Viburnum prunifolium.*

Composition.—(1) *Viburnin*, a glycoside. (2) A Resin. (3) Valerianic, tannic, and gallic acids.

Non-official Preparations

1. **Extractum Viburni Liquidum.**—1 in 1. *Dose.*—I to 2 drs. or 4 to 8 mils.
2. **Elixir Viburni et Hydrastis, B.P.C.** -Ext. Viburnum Liq. 50, Ext. Hydrastis 1.75, Ol. Coriander 0.50, Ol. Caraway 0.50, Glycerin to 100. *Dose.*—½ to 1 dr. or 2 to 4 mils.
3. **Extractum Viburni, B.P.C.**—Liquid extract by evaporation. *Dose.*—3 to 8 grs. or 0.2 to 0.5 grm.

Pharmacology and Therapeutics

It has been used as a sedative in neurotic and hysterical affections but its chief use is as an **uterine sedative.** It is supposed to diminish or check uterine contractions occurring during pregnancy and endangering its continuance, and it is therefore used in cases of **habitual abortion,** when this does not arise from any specific cause such as syphilis or nephritis. It is used extensively in all sorts of uterine troubles, but in therapeutic doses it is of no value at all.

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GROUP XV

DRUGS HAVING ANTIPYRETIC, ANTIPERIODIC AND ANTISEPTIC PROPERTIES

Class A: Antipyretics and Analgesics
Amidopyrine, Phenacetin, Phenazone, Acetanilide

Class B: Antiperiodics
Cinchona Bark, Quinine, Quinidine, Plasmochin, Atebrin

Class C: Antipyretics, Antiseptics and Antirheumatics
Salicylic Acid, Salicylates, Methyl Salicylas, Benzoin, Benzoic Acid, Benzoates

Antipyretics and Analgesics

Antipyretics or Febrifuges are remedies which lower the temperature of the body in pyrexia.

Antipyretics, except when given in toxic doses, have very little effect upon the temperature in health but they act powerfully when it has been raised above normal. The maintenance of the body heat at about 98.4°F. is the result of a fine adjustment between heat production on the one hand and heat dissipation on the other, and anything which disturbs this equilibrium will cause either a rise or a fall of temperature as the case may be. Heat is lost primarily from the skin and from the respiratory passages. From the skin by conduction and radiation, and by evaporation of sweat; and from the respiratory passages through warming of the inspired air, and by evaporation of water. A small amount is also lost in the excretion of urine and fæces. Excessive loss of heat is counteracted by (1) contraction of cutaneous vessels which by reducing perspiration diminishes the loss of heat, and (2) increased combustion of tissues, whereby more heat is formed. In order to preserve the equilibrium between these factors there exists a *heat regulating centre* situated in the basal ganglia of the cerebrum and in the neighbourhood of tuber cinereum. Any lesion in this neighbourhood is followed by a rise of temperature, *e.g.*, injury to corpus striatum. With the fall of temperature there is perspiration and flushing of the skin. The amount of oxygen absorbed and CO_2 given out are also diminished.

Antipyretics act in the following ways :—

1. *By increasing loss of heat by acting on the thermogenic centre in the corpus striatum.*—As phenacetin, amidopyrine acetanilide, phenazone, etc.

2. *By dilating the cutaneous blood-vessels and thus augmenting radiation.*—As alcohol, nitrites, spiritus ætheris nitrosi, salicylates (also act by diaphoresis), warm baths.

3. *By increasing the amount of perspiration* and thus causing a loss of heat by evaporation (*see Diaphoretics*).

4. *By abstracting heat.*—Cold or tepid water bath, cold wet-pack, cold sponging, local irrigation with cold water,

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cold water compress, and evaporating lotions are agents by which we can abstract heat and thus increase heat loss.

5. *By neutralising or destroying any specific poison causing pyrexia.*—As quinine in malarial fever, and antidiphtheritic serum in diphtheria.

Caloricrescents are remedies which elevate the body temperature. They may be local, as fomentation, poultices, etc., or general, which act as follows :—

(*a*) *By heat puncture, i.e.*, injury to the neighbourhood of corpus striatum. The rise of temperature is due to increased production and does not occur in glycogen-free animals.

(*b*) *Bacterial-toxins* when injected, or produced in the body by infection with living bacteria. Here the rise of temperature is due to diminished heat loss. Heat production is generally increased though not always so.

(*c*) *Certain drugs.* Tetrahydro β-naphthylamine causes rise of temperature of several degrees. There is increased heat production and diminished heat loss from cutaneous vaso-constriction. It is not a central effect as pyrexia occurs after the centre has been destroyed or made inactive by the previous use of antipyretics.

The temperature may be raised either by increased heat production or diminished heat loss. Pyrexia occurs only when the change exceeds the capacity of compensation. Belladonna, caffeine, cocaine, and picrotoxin in toxic doses also cause a rise of temperature.

AMIDOPYRINA

Amidopyrine. $C_{13}H_{17}ON_3$

Syn.—Pyramidon.

Source.—May be prepared by methylation of the reduction product of the nitroso-derivative of phenazone.

Characters.—Small, colourless crystals, or a white crystalline powder. No taste or odour. *Soluble* in 18 parts of water, and in 2 parts of alcohol (90 p.c.).

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

PHENACETINUM

Phenacetin

Syn.—Acetphenetidin.

Source.—Obtained by the acetylation of *p*-phenetidine.

Characters.—White glistening, crystalline scales, or a fine, white, crystalline powder. No odour; taste, slightly bitter. *Solubility.*—Very sparingly in cold water, more freely in boiling water, alcohol (90 p.c.); solution neutral.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Non-official Preparations

1. **Exalgin.** *Syn.—Methylacetanilide.*—Colourless acicular crystals. Antipyretic and analgesic. Chiefly used in *migraine, sciatica* and *neuralgias. Dose.*—½ to 2 grs. or 0·03 to 0.12 G.

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2. **Kryofin.**—A condensation product of para-phenetidin and methylglycolic acid. Analgesic and antipyretic, sometimes causing severe sweating, *Dose.*—8 to 15 grs. or 0.5 to 1 grm.

3. **Citrophen.** *Syn.—Phenetidin Citras.*—A dibasic para-phenetidin citrate. Acts like phenacetin. *Dose.*—3 to 8 grs. or 0.2 to 0.5 grm.

PHENAZONUM

Phenazone. $C_{11}H_{12}N_2O$

Syn.—Antipyrin.

Source.—It is 1-phenyl-2 : 3-dimethyl-5-pyrazolone. Obtained by the interaction of phenylhydrazine and ethyl acetoacetate, and subsequent methylation.

Characters.—Small, colourless crystals, or a white, crystalline powder ; odourless ; taste, slightly bitter. *Solubility.*—1 in 1·2 of water, 1 in 1.3 of alcohol (90 p.c.), or of chloroform.

Incompatibles.—Spiritus ætheris nitrosi, tannic acid and cinchona preparations. Powdered phenazone liquefies when rubbed with butyl chloral hydrate, sodium salicylate, naphthol.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Non-official Preparations

1. **Ferripyrin.** *Syn.—Ferropyrin.*—A compound of antipyrin 64 p.c. and iron 12 p.c. Useful in *chlorosis* and *anæmia.* 1 p.c. solution as *gonorrhœal* injection. *Dose.*—3 to 8 grs. or 0.2 to 0.5 grm.

2. **Salipyrin.** *Syn.—Antipyrin Salicylate.*—White, sweetish crystals, sparingly soluble in water. Analgesic, *antirheumatic. Dose.*—15 to 30 grs, or 1 to 2 grm.

3. **Acetopyrin.**—*Antipyrin Aceto-salicylas.* A white crystalline powder being a combination of phenazone and acetic acid. *Analgesic, antipyretic, anti-arthritic,* without injurious action on the heart. *Dose.*—8 to 15 grs. or 0.5 to 1 grm.

ACETANILIDUM

Acetanilide. C_8H_9NO (*Not official*)

Syn.—Phenyl-acetamide ; Antifebrin.

Source.—Obtained by the interaction of glacial acetic acid and aniline.

Characters.—Colourless, inodorous, glistening lamellar crystals ; taste, pungent. *Solubility.*—1 in 210 of cold, 1 in 18 of boiling water, 1 in 4·2 of alcohol (90 p.c.) ; freely in chloroform and ether.

Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

Pharmacology of Amidopyrine, Phenazone, Phenacetin and Acetanilide

Externally.—Both phenazone and acetanilide are local hæmostatics, but the latter is also an antiseptic.

Internally.—Blood is not affected by the ordinary doses, but its colour is changed by large doses, owing to the formation of methæmoglobin. Antipyrin seems to be devoid of this action. The red blood corpuscles are broken up, become distorted, shrunken and devoid of colouring matter, while part of methæmoglobin might escape through the kidneys, and hæmoglobin and even blood may appear in the urine. This effect is perhaps due to the decomposition of the drugs and the flooding of the tissues with paramidophenol, or the corresponding quinoline derivative.

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Heart.—In experimental work the heart muscle is first accelerated by ordinary doses, but in large doses the muscle is weakened and the beat becomes slow and irregular, causing collapse. This action is probably due to its sedative influence on the cardiac muscle. Acetanilide is the most depressant, next comes phenazonum, phenacetin and amidopyrine have little or no depressant action. Collapse occurring from moderate doses is often due to idiosyncrasy.

Blood-vessels.—Acetanilide and phenazone contract the blood-vessels by acting directly on their muscular fibres. These are therefore **hæmostatics**, phenazone being more energetic than the other. The blood-pressure is raised at first, and is lowered subsequently from cardiac weakness.

Respiration.—The respiratory force is diminished only by toxic doses.

Kidneys.—They slightly increase the flow of urine, urea and uric acid. Large doses cause hæmoglobinuria. Phenazone is quickly excreted and appears in the urine either unchanged or as oxyantipyrine in combination with glycuronic and sulphuric acids. Phenacetin appears as phenetidin compounds. Acetanilide is said to be excreted as aniline.

Skin.—Papular, erythematous, urticarial rashes are observed at times. They may produce a slight diaphoresis in health, but a copious one in pyrexia. Therefore they are **diaphoretics.**

Temperature.—They have very little effect in reducing the temperature in health, but are **powerful antipyretics** due to the fact that in fever the heat centre is in an abnormal state and is more susceptible to these drugs than normally. As a rule the temperature begins to fall within two hours and generally comes down to normal or even to subnormal and is accompanied by profuse sweating preceded by vasodilatation which is confined to the skin and is a central effect. This was at one time believed to be the cause of the fall, but the temperature falls even when the perspiration is checked by the previous use of atropine or agaricine. The antipyretic effect is the result of direct action on the heat regulating mechanism causing an increased heat dissipation by dilating the cutaneous vessels. In fact the perspiration is preceded by a feeling of external heat and flushing of the face.

Nervous system.—Their action on the nervous system is not well understood. They however act as powerful **analgesics**, and though not strongly hypnotic, yet taken at bedtime they favour the onset and maintenance of normal sleep. The pain sensation is abolished and unlike opium they do this without any appreciable effect on the mental activity. It has been suggested that the analgesia is the result of an action on synapses in the pain conveying tract in the thalamus adjacent to the heat centre. Acetanilide and phenazone

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sometimes cause convulsions and motor paralysis. The peripheral nerves and the nerve-endings are not affected even in poisoning.

Elimination.—These drugs are rapidly absorbed and eliminated. Acetanilide and phenacetin are mainly converted into paramidophenol. They are excreted in the urine and disappear from the body within 24 hours.

Toxic action.—Large doses cause great prostration, sometimes vomiting, weak, irregular pulse, slow respiration and sweating. In toxic doses these symptoms are aggravated leading to profuse sweating, cyanosis, collapse and death. Sometimes a rash appears on the skin. Poisoning may occur from phenazone and acetanilide. The writer had a case of poisoning from 30 grs. of phenacetin. Cyanosis of the face, mostly of the lips, hands and feet, and a slight depression were the only prominent symptoms.

Antidotes.—Warmth to the surface, stimulants, strychnine and atropine hypodermically, and oxygen inhalation.

Action of Phenazone and Phenacetin compared.—Phenazone is the best in respect of the efficacy, rapidity and certainty of its action, while phenacetin is safe, and its action more lasting, rarely producing subnormal temperature or collapse. Phenacetin has also a soothing and soporific action. Both of them cause profuse sweating *but do not shorten fever.*

Therapeutics of Amidopyrine, Phenazone, Phenacetin and Acetanilide

Externally.—Acetanilide and phenazone are occasionally used as a dusting powder, or as an ointment (20 grs. to 1 oz.) for chronic ulcers and eczema. A 10 p.c. solution of phenazone locally applied stops epistaxis.

Internally.—As **antipyretics** all are used to reduce fever-heat, but phenacetin, being the safest, is prescribed most frequently. They take about two hours to bring down the temperature, but phenazone and acetanilide do it most rapidly. To maintain the reduced temperature they require to be repeated every 4 hours, and this sometimes leads to dangerous symptoms on account of their depressing influence on the heart. They cannot control the duration of fever for as soon as the effects are over the fever rushes up again. Hence many physicians are averse to using them as antipyretics as a routine treatment, but they are very useful agents in cases where the temperature is so high as to endanger life, where the high temperature is the chief cause of distress, and where reduction of temperature and increased comfort are not counterbalanced by their masking the true condition of the disease. In hyperpyrexia they cannot be relied upon. Both phenazone and phenacetin have been given in every form of febrile condition with a high temperature, such as typhus, remittent, intermittent, puerperal fever, etc., but with unsatisfactory results. In fact one should not use drugs

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which act on the heat regulating mechanism, but should rely, for the reduction of temperature, upon those means which promote the dissipation of heat without influencing the centre.

As **analgesics** all these drugs may be given to relieve pain, but phenazone is the most powerful. For reasons already stated, phenacetin and amidopyrine will have the preference. There is hardly any pain which cannot be alleviated by phenazone. 5 to 10 grs. given hourly for 3 or 4 doses act like a charm in almost every form of headache and migraine. Phenacetin does it equally well in 5 gr. doses. Moreover, the pains of ataxy, sciatica, angina, internal aneurism, dysmenorrhœa are soon cut short by these drugs.

Phenacetin in 1 gr. doses is a useful hypnotic in the febrile diseases of children.

As a nervine sedative, phenazone is occasionally used in epilepsy, chorea, nocturnal emissions, laryngismus stridulus, asthma, sea-sickness, enuresis, etc.

Untoward effects.—Sometimes evidence of toxic manifestations are noticed following the use of antipyrin. These are chiefly due to idiosyncrasy. They are (1) erythematous or bullous eruptions with or without œdema of the skin, mucous membrane and glottis; (2) gastric intolerance, avoided by combining with alkalies; (3) profuse perspiration, subnormal temperature and a tendency to collapse, specially in tubercular and cachectic patients; (4) cyanosis, fall of blood-pressure and intermittent pulse; (5) albuminuria, specially after long continued use.

Prescribing hints.—All these may be given in powders, cachets or capsules. Phenazone being soluble in water can be given in peppermint water which disguises its taste, while the others can be suspended by compound tragacanth powder. Sometimes they may be given with advantage in brandy or whisky. The student should remember that calomel when triturated with antipyrin forms a toxic compound, and with chloral and sodium salicylate form oily liquids. The solubility of the salts of quinine and caffeine is increased by the addition of antipyrin. On account of a long list of incompatibles phenazone is better given alone.

Antiseptics and Antirheumatics

ACIDUM SALICYLICUM

Salicylic Acid. $HC_7H_5O_3$

Source.—May be obtained by the interaction of sodium phenate and carbon dioxide. Contains not less than 99.4 p.c. of $C_7H_6O_3$.

Characters.—Colourless crystals, or light feathery crystalline powder, almost odourless; taste, sweetish and acrid. *Solubility.*—1 in 500 of water, 1 in 3½ of alcohol (90 p.c.), readily in ether.

Incompatibles.—Iron salts, quinine sulphate, nitric ether, and Spt. ammon. aromat.

B. P. Dose.—5 to 10 grs or 0.3 to 0.6 grm.

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Official Preparation

1. **Unguentum Acidi Salicylici.**—2 p.c.

SODII SALICYLAS

Sodium Salicylate. $NaC_7H_5O_3$

Source.—Obtained by the interaction of salicylic acid and sodium carbonate. It contains not less than 99.5 p.c. of pure sodium salicylate.

Characters.—Colourless, small crystals or crystalline flakes, or a white powder; odourless, or with a faint characteristic odour; taste, sweetish, saline, unpleasant. *Solubility.*—1 in 1 of water, 1 in 6 of alcohol (90 p.c.).

Incompatibles.—Acids, antipyrin, quinine and iron salts.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm.

ACIDUM ACETYLSALICYLICUM

Acetylsalicylic Acid. $C_9H_8O_4$

Syn.—Aspirin.

Source.—Obtained by the action of acetic anhydride or of acetyl chloride on salicylic acid. Contains not less than 99.5 p.c. of $C_9H_8O_4$.

Characters.—Small, colourless, acicular crystals, or a white crystalline powder. Odourless; taste, slightly acid. Stable in dry air, but in contact with moisture gradually hydrolyses into acetic and salicylic acids. *Soluble* in 300 parts of water, in 5 parts of alcohol (90 p.c.), and strong solution of ammonium acetate.

B. P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Non-official Preparations and Derivatives of Salicylic Acid

1. **Ammonii Salicylas, U.S.P.**—In colourless, lustrous, monoclinic crystals, prisms or plates, or a white crystalline powder. Taste, slightly saline and bitter, afterwards sweetish. No odour. *Dose, U.S.P.*—1 grm. or 15 grs.

2. **Calcii Aceto-salicylas.** *Syn.—Tylcalsin.*—White amorphous, non-hygroscopic powder. Soluble 1 in 6 of water but dissociates in solution. *Dose.*—5 to 15 grs. or 0.3 to 1 grm. *Antirheumatic* and *influenza specific.* Combines the good effects of sodium salicylate and aspirin.

3. **Ferri-Salicylas.**—Antiseptic, astringent. *Dose.*—3 to 10 grs. or 0.2 to 0.6 grm.

4. **Collodium Salicylicum Co.** *Syn.—Corn Paint.*—Salicylic Acid 12, Extract of Indian Hemp 2, Acetone 30, Acetone Collodion to 100. A painless solvent for hard and soft corns.

5. **Injectio Sodii Salicylatis.**—1 in 20 of sterile water. Injected into the seat of pain in *rheumatism. Dose.*—15 to 30 ms. or 1 to 2 c.c.

6. **Salacetol.** *Syn.—Acetyl methyl-salicylate.*—A compound obtained by heating monochlor-acetone and sodium salicylate. As an intestinal antiseptic in diarrhœa, in doses of from 10 to 30 grs. in castor oil before breakfast.

7. **Salophen,** *Syn.—Acetyl-para-amido-phenol salicylate.*—Whitish, tasteless crystals, insoluble in water. It is unaffected by gastric juice, but is decomposed by the pancreatic secretion. Has a quicker action in acute rheumatism than salicylic acid. *Dose.*—10 to 15 grs. in cachets.

8. **Aspriodine.** *Syn.—Acetyl Iodo-salicylic Acid.*—Contains 41.47 p.c. iodine and 58.53 p.c. aspirin radical. Embodies the properties of iodides and aspirin. Useful in *rheumatic affections, arteriosclerosis, asthma, scrofula* and *enlarged glands. Dose.*—5 grs. daily after food.

9. **Sedasprin.** *Syn.—Acetyl Bromo-salicylic Acid.*—A similar compound with 30.86 p.c. bromine. Combines the sedative action of bromides. *Dose.*—5 to 10 grs. or 0.3 to 0.6 grm.

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SALICINUM

Salicin. $C_{13}H_{18}O_7$

Source.—A crystalline glucoside obtained from the bark of various species of *Salix*, and of *Populus*.

Characters.—Colourless crystals, or white crystalline powder. Taste, bitter. *Solubility.*—1 in 28 of water, 1 in 80 of alcohol (90 p.c.), insoluble in ether.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Pharmacology of Salicylic Acid and Salicin

Externally.—Salicylic acid and salicin are antiseptics, but the acid is the most powerful. A 2 p.c. solution of the acid kills bacteria and checks fermentation, but its salts have no antiseptic properties. Salicylic acid is a powerful local anhidrotic. Applied to the nose it causes sneezing and cough. It has a special action on the epithelium and in dilute form the acid acts as a keratoplastic agent, and aids regeneration of new epithelium. In a concentrated form it acts peculiarly on the epidermis specially the corneous layer, and the horny cells are softened, gradually loosened and separated without much inflammatory reaction.

Internally. **Alimentary canal.**—Salicylic acid is an irritant to the stomach, and when taken undiluted causes pain, nausea and vomiting. Sodium salicylate and salicin are less irritant. Salicin is a bitter, stomachic tonic. Salicin is transmitted unchanged into the intestine, where it is broken up probably by the help of the pancreatic juice. Salicin is partly converted into saligenin and glucose, and saligenin again into salicyluric, salicylous and salicylic acid. Acid acetylsalicylic passes through the stomach unchanged and therefore does not act as an irritant here, but is decomposed partly into salicylic acid in the gut and is absorbed as sodium acetyl salicylate.

Blood.—Salicylic acid enters the blood as sodium salicylate, which, at any rate, is the form in which it is found in the blood. Some think it exists as an albuminate, but of this there is no proof. It is possible that sodium salicylate is converted again into salicylic acid by carbonic acid in the inflamed joints. However, the fact remains that a portion of the salicylic acid of the salicylate unites with glycocoll either in the blood or tissues to form salicyluric acid ; thus $HC_7H_5O_3$ (salicylic acid)$+C_2H_5NO_2$ (glycocoll)$=HC_9H_8NO_4$ (salicyluric acid)$+H_2O$. This chemical change is identical with what happens in the conversion of benzoic acid into hippuric acid.

Heart and blood-vessels.—In therapeutic doses salicylic acid, sodium salicylate and salicin have very little effect on circulation. Very large doses make the heart slow and weak, the muscles get relaxed and dilated causing a fall of pressure. The idea that they depress the heart was based

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on observations made with artificial preparations which occasionally contained orthocresotic acid, a powerful cardiac depressant. Physiologically pure artificial salt is not depressant.

Temperature.—The salicylates in moderate doses reduce febrile temperature, due to increased heat dissipation from cutaneous dilatation, aided by perspiration. In healthy individuals this is compensated by increased heat production, so that the normal temperature is not easily affected. They are therefore antipyretics. A single dose of 20 to 30 grs. of sodium salicylate may bring down the temperature of 105°F. to 101°F. in 2 or 3 hours.

Skin.—Salicylic acid, aspirin and sodium salicylate increase perspiration due to (1) dilatation of the cutaneous vessels, and (2) according to Cushny to increased activity of the sweat centre. Dilatation of the skin vessels may cause some skin rashes to appear.

Liver.—The salicylates are efficient biliary antiseptics. They increase the secretion of bile, possibly from some specific action on the liver cells. The bile is rendered thin and watery. There is however a total increase in the solids of the bile. In this respect the action of sodium salicylate resembles that of sodium benzoate.

Nervous system.—Their action on the nervous system is ill-understood. They produce a train of symptoms identical with cinchonism (*see* salicylism).

Kidneys.—Salicylic acid is excreted in the urine as salicyluric acid and sodium salicylate. It can be detected in the urine within 10 to 30 minutes after ingestion. It sometimes causes nephritis with bloody and albuminous urine. Large doses increase the excretion of urea and uric acid, and give sometimes to the urine a greenish colour due to the presence of pyrocatechin. It renders the urine **antiseptic** and **increases its acidity**. The urine of patients taking salicylic acid gives a purple colour on the addition of solution of ferric chloride.

Uterus.—Some think that salicylic acid is an **emmenagogue** and causes abortion, but there is no sufficient evidence to confirm this statement.

Elimination.—Salicylates are excreted to some extent in all the secretions, chiefly by the urine, and to a less extent by the sweat, saliva, bile, sputum and fæces. The excretion begins within 15 minutes and is practically completed in 6 to 48 hours. The rapid excretion explains the necessity of large and repeated doses.

Aspirin is about one and one-half times more toxic than sodium salicylate. Even small doses (5 to 10 grs.) occasionally produce alarming symptoms. It is however a stronger analgesic and antipyretic due to the undecomposed acetyl compound entering the nerve cells more rapidly.

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Toxic action.—The symptoms resemble cinchonism, buzzing in the ears, disturbed hearing and vision, headache, vertigo, mental confusion from disturbance of circulation of the brain are the early symptoms. When these appear further use of the drug should be stopped. If however it is pushed further, nausea, vomiting, deafness, delirium, flushed face, free perspiration, rapid pulse, deep and accelerated respiration and air hunger may be present.

The disorders of hearing have been ascribed to congestion of the tympanum, although some attribute it to the same causes as in quinine, *i.e.* changes in the nerve cells in the ear. Similarly the impairment of sight is due to vascular and retinal changes in the eye.

All the symptoms of salicylism have been attributed to a marked disturbance in acid-base equilibrium and formation of **non-gaseous acidosis** and does not occur when the drug is used with sufficient alkali. This acidosis is the result of increased production of acids combined with defective excretion due to a damaged kidney.

Therapeutics of Salicylic Acid and Salicin

Externally.—Salicylic acid is largely employed in surgical practice in the form of a lotion, ointment, lint, cotton, etc. Small epitheliomas and chancres soon heal when pure acid is daily dusted over them. In lupus, corns and tylosis collodium salicylicum is a useful application. A hot strong solution is recommended in acne, and an ointment containing $\frac{1}{2}$ dr. of carbolic and salicylic acids each in 1 oz. cures ringworm. Being non-volatile it is not an effective antiseptic for deep suppurating wounds. Salicylic acid and talc powder is an excellent application for checking excessive sweating in phthisis, and fetid perspiration of the feet and armpits. A 1 to 4 p.c. solution or an ointment (1 to 6) often checks the itching of eczema, intertrigo and urticaria.

Internally.—Salicylic acid is locally applied to diphtheritic membranes. It is used as an internal antiseptic in sarcinous vomiting and fermentative dyspepsia.

As an *antirheumatic*, salicylic acid and the salicylates are considered specifics for **acute rheumatism**, possibly by the setting free of salicylic acid in the inflamed part by the carbonic acid in it. They reduce the temperature, lessen the swelling, and relieve the pain, if 20 to 30 grains are given every 2 hours, until 1 to 6 doses are swallowed, and then at longer intervals. In these cases it is often combined with large doses of bicarbonate of soda to lessen gastric irritation. Even after an apparent cure they should be continued for one or two weeks. The liability to cardiac complications is minimised by salicylic acid treatment, although some authorities aver that the tendency to both endocarditis and pericarditis is greatly increased by the use of salicylates in acute rheumatic fever. Sodium salicylate may also be used as subcutaneous or intravenous injection. The intravenous route is safe and painless and is best suited for cases where the drug is not well tolerated when given by the mouth or causes no improvement. The following solution may be used, *viz.*—sodium salicylate (pure) 2 drs. or 8 grm. in freshly steri-

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lised distilled water 50 c.c. or 1⅔ oz. Of this 2 c.c. is injected once or twice a day. If necessary ½ dr. or 2 grm. of caffeine sodium benzoate may be added to the above solution. In the hyperpyrexia of rheumatism salicylates are of no use. In chronic rheumatoid arthritis, gout, gonorrhœal rheumatism, opinions differ as to their utility. As an antirheumatic aspirin is inferior to the salicylates, but is frequently of some value in chronic cases, since it is usually better borne and is probably more slowly eliminated.

As an *antipyretic*, sodium salicylate and salicin may be usefully employed in typhoid, remittent, intermittent and inflammatory or specific fevers. Sodium salicylate 3 grs. given hourly gives better results in quinsy than aconite. Aspirin is more freely used in the form of tablets for colds, sore-throat, headache and influenza.

Intravenous injection has been used with success in psoriasis (10 c.c. of a 20 p.c. solution) given three times a week for 4 to 5 weeks, and in encephalitis lethargica.

Recently its use has been highly recommended in the injection treatment of **varicose veins**. For this 3 c.c. of a 20 p.c. solution is injected into the vein, the varices being first made empty of blood. One injection generally suffices, but if necessary this is followed, a week later, by another injection of 30 p.c. solution. If combined with 10 p.c. sodium chloride these injections are practically painless.

As a hepatic stimulant, all these drugs may be given in torpidity of the liver and catarrhal jaundice, but sodium salicylate is the most effective. Sodium salicylate and aspirin are both useful in the treatment of hepatic colic, and are given with benefit as solvents of gall-stones.

As an analgesic, sodium salicylate may be given in neuralgias and lumbago, and is considered to be an effective remedy for sciatica. In chronic sciatica it gives the best result when combined with iodide. It has been extolled in chorea, but it seems that unless associated with an attack of rheumatism, recent or remote, it has no specific action in this disease. As an analgesic aspirin is superior to sodium salicylate and resembles the drugs of the phenacetin group.

Sodium salicylate and aspirin have been found to reduce the quantity of sugar in the urine in diabetes.

Prescribing hints.—Sodium salicylate is best given in solution. If mixed with ammonia the mixture gradually turns from pale-yellow to brown on exposure to air. When given with quinine or citric acid, precipitation occurs. Theoretically aspirin should not be prescribed with bicarbonate of soda, but the bicarbonate lessens the nausea and heartburn which sometimes result from its use. Aspirin is best administered in cachets, tablets or in powders. Alcoholic solutions decompose it to salicylic acid and acetic acid on standing. It may be given in milk to children.

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On account of the rapid elimination the quantity required should be divided into several doses and given every three or four hours. When treating cases of rheumatism with large doses, the salt should be freely diluted and combined with bicarbonate of soda to avoid irritation of the stomach. The full dose should be continued for three days after subsidence of the pain and temperature, and then gradually reduced. The sweetish taste of sodium salicylate is unpleasant and nauseating to many patients. Bromides lessen the tendency to salicylism. It cannot be prescribed in an acid solution as salicylic acid is formed which is insoluble. Salicin is not freely soluble in water but the addition of glycerin increases its solubility. For application to joints methyl salicylate is generally used either undiluted or mixed with olive oil.

Caution.—The natural or the physiologically pure artificial salts are only to be used. They should be given with caution to children, old and weak individuals, and to persons suffering from cardiac and renal diseases. The administration of the drug is to be suspended if headache, deafness and ringing in the ears show themselves.

METHYLIS SALICYLAS

Methyl Salicylate. $C_8H_8O_3$

Syn.—Artificial Oil of Wintergreen.

Source.—Obtained by the esterification of methyl alcohol and salicylic acid. Contains not less than 98 p. c. of pure methyl salicylate.

Characters.—A colourless, or pale yellow liquid. Characteristic, aromatic odour; taste, sweetish, warm, aromatic. Slightly soluble in water, freely in alcohol (90 p.c.). Sp. gr. 1.186 to 1.191.

B.P.Dose.—5 to 15 ms. or 0.3 to 1 mil.

Non-official Preparations and Derivatives

1. **Linimentum Methyl Salicylatis, B.P.C.**—Menthol 5, oil of eucalyptus 10, Rectified oil of camphor 25, methyl salicylate to 100. As a paint over *rheumatic joints* and *neuralgic areas,* the parts being covered with oil silk.
2. **Ung. Methylis Salicylatis Co., B.P.C.** *Syn.—Analgesic Balsam.*—Methyl salicylate 50, menthol 10, eucalyptol and oil of cajuput (by wt.) each 2.5, white beeswax 20, lanoline 15. In *sciatica, lumbago* and *rheumatism.*
3. **Mesotan.**—*Methoxy-methylester of Salicylic Acid.*—An inunction of 1 part of mesotan with 2 parts of olive oil is very useful in *rheumatism and gout,* especially if combined with the internal administration of aspirin.

Pharmacology and Therapeutics

The action and uses of methyl salicylas are much the same as those of the salicylates. As it is absorbed by the unbroken skin it is used externally. It may also be used internally in capsules.

BENZOINUM

Benzoin

Syn.—Gum Benjamin; Sumatra Benzoin. Syn. I. V.—*Loban.*

Source.—A balsamic resin obtained from the incised stem of *Styrax Benzoin.*

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Characters.—In hard brittle masses consisting of numerous whitish or reddish tears embedded in a greyish-brown or reddish-brown translucent matrix. Odour agreeable; taste, slightly acrid. When heated it melts and evolves whitish fumes with an irritating odour.

Composition.—(1) *Benzoic acid* 18 p.c. (2) *Cinnamic acid* 20 p.c. (3) *Volatile Oil.* (4) *Resins.*

Official Preparation

1. **Tinctura Benzoini Composita.** *Syn.—Friar's Balsam.*—**B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

ACIDUM BENZOICUM

Benzoic Acid. $C_7H_6O_2$

Source.—Obtained from benzoin, or prepared synthetically.

Characters.—In light feathery, colourless and odourless crystals. *Solubility.*—1 in 450 of cold water, 1 in 3 of alcohol(90 p.c.), freely in chloroform and ether.

Incompatibles.—Ferric salts and mercuric chloride.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Enters into.—Tr. Opii Camphorata.

SODII BENZOAS

Sodium Benzoate. $NaC_7H_5O_2$

Source and characters.—A white, inodorous, amorphous, or subcrystalline powder with a faint benzoic odour. Taste, unpleasant, sweetish and saline. Prepared by neutralising benzoic acid with sodium carbonate. *Solubility.*—1 in 2 of water, slightly in alcohol (90 p.c.).

B.P. Dose.—5 to 30 grs. or 0.3 to 2 grms.

Non-official Derivatives of Benzoic Acid

1. **Cryogenin.** *Syn.—Meta-benzamine semicarbazide.*—A crystalline body sparingly soluble in water, used in *pyrexia of phthisis* and *enteric fever.* Has no depressing action. *Dose.*—5 to 15 grs. or 0.3 to 1 grm.

2. **Sodii Hippuras.**—A soluble white amorphous powder. A solvent of urates in *gout* and *gravel*, and to lower *blood-pressure.* *Dose.*—5 to 30 grs. or 0·3 to 2 grm.

3. **Calcii Hippuras.**—Shining white crystals. *Dose.*—5 to 30 grs. or 0.3 to 2 grm.

4. **Benzyl Benzoate.** *Syn.—Spasmodin.*—An ester of benzyl alcohol and benzoic acid. Used in diarrhœa and dysentery; intestinal, renal and biliary colic; spastic constipation and any spasmodic condition. *Dose.*—10 to 30 ms. of 1 in 5 alcoholic solution in water or emulsion.

Pharmacology of Benzoin and Benzoic Acid

Externally.—Both benzoin and benzoic acid are antiseptics, superior to carbolic and salicylic acids. A concentrated solution is a local stimulant and irritant.

Internally. **Gastro-intestinal tract and liver.**—The salts are less irritant and are therefore used in preference to the acid. In small doses they have little effect on the stomach and intestine, but in large doses irritate them. They are hepatic stimulants increasing both the quantity and solids of the bile. The acid is an intestinal disinfectant.

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Respiratory tract.—Both the gum and the acid cause sneezing when inhaled. Their vapour directly stimulates the bronchial secretion which is also remotely stimulated during their excretion when given by the mouth. Hence they are **expectorants.** They also disinfect the secretion.

Urinary tract.—Benzoic acid and its salts are largely excreted with the urine, partly unchanged, but chiefly as hippuric acid. Occasionally succinic acid also appears in the urine. The appearance of hippuric acid in the urine is due to the decomposition of benzoic acid in the presence of glycocoll in the renal cells but not in the blood. Glycocoll or glycine is amino-acetic acid and may be obtained by hydrolysing gelatin with hot hydrochloric acid and separating from other amino-acids. It occurs as a constituent of many proteins. The conversion of the benzoic acid taking place in the kidneys is proved by the following experiments :—(1) If benzoic acid is given in large doses, it is found unchanged in the blood, and if the renal arteries are tied no hippuric acid is generated, though it is formed if the ureters are tied. (2) Benzoic acid is converted into hippuric acid if the blood containing the former but no glycocoll is slowly passed through the kidneys immediately removed after death. (3) When hippuric acid is given by the mouth, benzoic acid is detected in the blood and hippuric acid in the urine. Hippuric acid thus formed performs most important functions. It stimulates the activity of the renal cells and renders the alkaline urine acid. Hence benzoic acid and benzoates are diuretics and acidifiers of alkaline urine. Over the mucous membrane of the urinary tract they have a soothing and disinfecting influence.

Temperature.—Benzoic acid and benzoates are antipyretics sometimes acting more powerfully than salicylic acid, but how they act is not known.

Metabolism.—They increase metabolism and there is excess of nitrogenous constituents of urine, and the body weight falls. Benzoic acid reduces the excretion of uric acid.

Elimination.—Chiefly with the urine, and partly with the sweat, saliva and bronchial secretion, which are stimulated to a slight extent.

THERAPEUTICS

Externally—A piece of lint soaked in Friar's balsam may be used to stop bleeding from, and promote the healing of, fresh wounds. In the same manner it may be used as an effective dressing for ulcers of all sorts. Undiluted Friar's balsam injected into sinuses establishes a healthier action in these tracts and heals them quickly. Locally applied, it relieves the pruritus of urticaria, and in solution (5 p.c. of the compound tincture with 5 p.c. of glycerin in water) it is a soothing stimulant application for the skin after the cure

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of acne. Benzoin is mixed with lard to prevent its decomposition, but it occasionally causes irritation of the skin.

Internally. **Lungs.**—Both benzoin and benzoates are largely employed either by the mouth or as an inhalation, in chronic bronchitis and phthisis, particularly if the expectoration is foul and scanty. The vapour of the tincture has been found to cut short, with surprising rapidity, attacks of catarrh and influenza.

Urinary tract.—As an *acidifier* of alkaline decomposing urine in cystitis or pyelitis, and in phosphatic calculi, benzoic acid and benzoates are most valuable. The salts should be used in preference to the acid, as they cause less gastro-intestinal irritation. They may be combined with urinary sedatives, such as tincture of hyoscyamus.

Rheumatism and gout.—Benzoate of soda may be given in acute rheumatism when salicylate of sodium cannot be borne or fails to do good. In gout it is occasionally used with the idea that it converts uric acid into hippuric acid and thus helps its elimination.

Prescribing hints.—The acid may be given in cachets, pills, or mixture suspended by mucilage. With acids the benzoates are decomposed into insoluble benzoic acid, and with ferric salts form insoluble flesh coloured ferric benzoate. They are also incompatible with lead, silver and mercury. Most alkaloids form insoluble benzoates. The vapour may be inhaled through an inhaler or even directly from a bottle.

GROUP XVI

CHEMOTHERAPEUTIC AGENTS

Before proceeding with the discussion of the individual drugs of this group it is necessary to describe the Reticulo-endothelial System, which modern research has shown to influence the action of drugs in the treatment of different infectious diseases. Evidence is accumulating in favour of the view that drugs, which are supposed to have a specific action, in the majority of instances, act in an indirect way through the different tissues of the body particularly through the cells of the reticulo-endothelial system. Many drugs act as specifics within the body of the host while possessing little or no such effect outside the body. Moreover, certain drugs are rapidly eliminated by the body, and in dilutions in which they occur in the blood and tissues after the administration in therapeutic doses, it is impossible to exert any direct action on the parasites. In fact it has been shown (*see* page 65) that the co-operation of the host is an important factor in the production of the specific action of a drug. It has therefore been suggested that this system is responsible for the formation of the natural defensive mechanism, which is an important factor in the causation of cures

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in different infections, and dysfunction of this system by 'blockade' or splenectomy experiments reduces or even completely abolishes the therapeutic value of a drug.

The exact manner in which the system responds to the stimulus of the specific drug depends upon the nature of the infecting organism. While some parasites are rapidly destroyed by phagocytes, others require to be disposed of by the destructive action of the lytic antibodies. In the first instance the response is evidenced by mobilisation and functional activation of the phagocytic cells of the system, while in the case of the other there is increased antibody production. When both these methods are of little use, the system utilises other methods, one being the elaboration of a powerful parasiticidal substance from the drug used. The modern conception of the specific action of a drug is that it stimulates the natural processes of the body in the cure of disease by bringing about such changes, directly or indirectly, either on the parasite or its environment as would be conducive to the success of the natural processes at work.

The different ways in which this system helps drugs in acting as specifics are as follows:—

1. By acting as a store-house for the drug and elaborating it slowly as required, thus preventing its rapid escape from the body and ensuring continuous supply.
2. By carrying the medicament to the neighbourhood of the lesion where it is most needed.
3. By possibly forming new compounds with greater parasiticidal properties.
4. It is possible that the drug stimulates the system in the production of more pronounced and effective phagocytic action and formation of antibodies. In fact Krishnan* has definitely shown that the phagocytic power of the cells of this system is stimulated by quinine in the treatment of malaria which accounts for the cure of the disease.

The reticulo-endothelial system is composed of a special group of cells of mesenchymal origin and of the macrophage or large mononuclear type possessing the property of phagocytosis and intracellular digestion. These cells are found in the liver, spleen, bone marrow and lymphatic glands, and to a greater or lesser degree in other parts of the body. The cells composing this system are of six types of which *monocytes* and *histiocytes* or *clasmatocytes* possess powerful phagocytic properties. Both in health and disease this system performs diverse important functions of which phagocytosis is perhaps the chief and most important one, and it is possible that most of its other functions more or less depend upon this property.

* Krishnan, *Indian Journal of Medical Research.* Oct. 2, 1933.

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The different functions of the reticulo-endothelial system may be classified as follows:—

1. *Formation of bile pigment.*—It is now recognised that bile pigment is formed in all tissues in which reticulo-endothelial cells are present including Kupffer's cells in the liver, but not by the glandular cells of that organ.

2. *Destruction and regeneration of red cells.*—It has been shown that the cells of this system take up for purposes of destruction those red cells whose alloted span of life is over, or those that have become damaged as a result of some inflammatory processes, toxins or parasitic invasion. Along with destruction there is also regeneration, and these two processes go hand in hand so that the red cell count is maintained at a constant level. In fact this system supplies the stimulus for regeneration of red cells, and in the absence of such stimulus the bone-marrow fails to manufacture sufficient number of red cells to maintain the equilibrium.

3. *Iron metabolism.*—Closely related to the regeneration of the red cells is the property of this system to utilise the iron from the degenerated red cells and hæmoglobin for the formation of fresh red cells. This metal is stored in the liver and spleen by the reticulo-endothelial cells which is metabolised in the synthesis for the manufacture of hæmoglobin.

4. *Cholesterol metabolism.*—Experimental evidence goes to show that storage of cholesterol is another important function of this system.

5. *Phagocytosis of bacteria and particulate substances.*—Experimental observations have shown that this system has the property of engulfing different bacteria and other organisms, *e.g.* protozoa, and carry them to internal organs, like the spleen and liver, for purposes of destruction. In many infectious diseases these cells have been found to be actually loaded with different organisms in infected tissues. Apart from the destruction of different bacteria and other organisms there is enough evidence to show that these cells readily ingest substances like Indian ink particles, vital dyes, carbon, colloidal particles of arsenic, antimony, bismuth and mercury.

The drugs belonging to this group are largely used as specifics in certain protozoal diseases and may be classified as follows:—

Class A: Drugs used in Malaria
Cinchona and its alkaloids, **Plasmochin, Atebrin**

Class B: Drugs used in Syphilis
Mercury, Bismuth, Arsenic, Iodides

Class C: Drugs used in Leishmaniasis
Antimony and its compounds

Class D: Drugs used in Trypanosomiasis
Pentavalent compounds of **Arsenic (atoxyl), Tryparsamide, Bayer 205**

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Class E : Amœbicidal remedies

1. **Ipecacuanha, Emetine, Emetine-Bismuth-Iodide, Gavano** (*see* page 298)
2. Certain Organic Arsenic Compounds : **Stovarsol, Carbarsone**
3. **Kurchi** and its alkaloids
4. Oxyquinoline Derivatives and certain Dyes : **Yatren, Rivanol**

Class A : **Antimalarial remedies**

CINCHONA

Cinchona

Syn.—Cinchonæ Rubræ Cortex ; Red Peruvian Bark.

Source.—The dried bark of the cultivated trees of *Cinchona Calisaya, Cinchona Ledgeriana, Cinchona officinalis, Cinchona succirubra*, and of hybrids of either of the last two species with either of the first two. Contains not less than 6 p.c. of the total alkaloids of cinchona, of which not less than one-half consists of quinine and cinchonidine.

Characters.—In quilled or curved pieces, up to 30 cm. or more long ; 2 to 6 mm. thick; outer surface, grey or brownish-grey ; tough from longitudinal ridges, transversely cracked and warty; inner surface brick-red, coarsely striated. Fracture, shortly fibrous. Powder, brownish or reddish-brown. Slight odour. Taste, bitter, somewhat astringent.

Composition.—A. *Four important alkaloids.*—(1) *Quinine*, as a hydrate. (2) *Cinchonine.* (3) *Quinidine.* (4) *Cinchonidine.* These alkaloids are bases and behave like alkalies. B. *Three acids.—Quinic acid*, closely allied to benzoic acid. (2) *Quinovic Acid.* (3) *Quinotannic Acid.* C. *One glycoside.—Chinovin*, which easily splits up into chinovic acid and glucose. *Cinchona red. One volatile oil* which gives the bark its smell.

Incompatibles.—Ammonia, lime water, metallic salts and gelatin.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Official Preparations

1. **Extractum Cinchonæ.**—Contains 10 p.c. of the alkaloids, or $\frac{1}{5}$ gr. in 8 grs. **B.P. Dose.—2 to 8 grs. or 0.12 to 0.5 grm.**
2. **Extractum Cinchonæ Liquidum.**—Contains 5 p.c. w/v of the alkaloids of cinchona, or $\frac{3}{4}$ gr. in 15 ms. **B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**
3. **Tinctura Cinchonæ.**—Contains 1 p.c. w/v of the alkaloids of cinchona, or $\frac{3}{5}$ gr. in 60 ms. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**
4. **Tinctura Cinchonæ Composita.**—Contains 0.5 p.c. w/v of the alkaloids of cinchona, or $\frac{1}{4}$ gr. in 60 ms. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Non-official Preparations

1. **Cinchona Febrifuge.**—Contains crystallisable quinine 7.40 p.c., cinchonine 18.58 p.c., cinchonidine 5.84 p.c., quinidine 29.83 p.c., colouring matter 5. *Dose.*—1 to 10 grs. or 0·06 to 0·6 grm.

2. **Cinchonidinæ Sulphas, U.S.P.**—In colourless, silky crystals, soluble in water. *Dose, U.S.P.*—0.15 grm. or 2½ grs.

3. **Cinchoninæ Sulphas.**—The sulphate of an alkaloid obtained from several species of cinchona. In white lustrous prismatic crystals. Odourless with a bitter taste. *Dose.*—1 to 10 grs. or 0.06 to 0.6 grm.

Pharmacology and Therapeutics

Internally.—Cinchona bark is an astringent, bitter tonic, a febrifuge and a mild antiperiodic, due to the alkaloids and

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other ingredients it contains. The crude bark irritates the stomach and bowels. It is often prescribed with other vegetable bitters during convalescence from an acute febrile attack, or along with quinine salts to increase their anti-periodic property. Combined with Spiritus Ammoniæ Aromaticus the compound tincture makes an excellent "Pick-me-up." It also checks the craving for strong drinks.

Owing to its high quinidine content cinchona febrifuge is specially valuable in benign tertian infection. But owing to the presence of cinchonidine it has the disadvantage of causing vomiting. It is best given two and a half hours after food in *cachets, tablets* or in *mixture* with citric acid. The vomiting may be checked by the previous use of 10 ms. of solution of adrenaline chloride. With cinchona febrifuge relapses are less, and given with alkalies some consider it more effective than quinine. But according to Sinton it gave 73.1 p.c. relapses in simple tertian infection. The consensus of opinion is that provided its composition is standardised, it is but little inferior to quinine both in the production of clinical and radical cure, and is certainly cheaper. In order therefore to supply such a standardised preparation Totaquina has been introduced, which contains 70 p.c. of the total alkaloids of which not less than one-fifth is quinine. The strength of this preparation even varies, but it is fairly reliable.

TOTAQUINA

Totaquine

Source.—Is a mixture of alkaloids from the bark of *Cinchona succirubra*, *Cinchona robusta*, and other suitable species of *cinchona*. Contains not less than 70 p.c. of crystallisable cinchona alkaloids of which not less than one-fifth is quinine. Resembles cinchona febrifuge.

Characters.—A nearly colourless, or pale yellowish-grey or pale brown powder; no odour; taste, bitter. Almost *insoluble* in water, almost completely soluble in warm alcohol (95 p.c.).

B.P. Dose.—1 to 10 grs. or 0.06 to 0.6 grm.

QUININAE HYDROCHLORIDUM

Quinine Hydrochloride. $C_{20}H_{24}N_2O_2,HCl,2H_2O$

Source.—Is the hydrochloride of an alkaloid, quinine, obtained from the bark of various species of Cinchona.

Characters.—Colourless, glistening needles; efflorescent in warm air; no odour; taste, very bitter. *Solubility.*—1 in 32 of water, 1 in 2 of alcohol (90 p.c.).

B. P. Dose.—1 to 10 grs. or 0.06 to 0.6 grm.

QUININAE DIHYDROCHLORIDUM

Quinine Dihydrochloride. $C_{20}H_{24}N_2O_2,2HCl$

Syn.—Acid Quinine Hydrochloride.

Source.—Is the acid hydrochloride of the alkaloid, quinine, obtained from the bark of various species of cinchona.

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Characters.—A white amorphous powder. *Solubility.*—In 0.6 parts of water and in 12 parts of alcohol (90 p.c.). Reaction acid.

B.P. Dose.—1 to 10 grs. or 0.06 to 0.6 grm; 5 to 10 grs. or 0.3 to 0.6 grm. (intravenous or intramuscular injection).

QUININAE SULPHAS

Quinine Sulphate. $(C_{20}H_{24}N_2O_2)_2,H_2SO_4,7\frac{1}{2}H_2O$

Source.—The same as that of quinine hydrochloride.

Characters.—Colourless, glistening, silky needles; taste, intensely bitter. *Solubility.*—1 in 800 of water, giving the solution a bluish fluorescence; entirely in water acidulated with a mineral acid.

Incompatibles.—Alkalies and their carbonates, astringent infusions.

B.P. Dose.—1 to 10 grs. or 0.06 to 0.6 grm.

Official Preparations

1. **Liquor Quininæ Ammoniatus.** *Syn.—Tr. Quininæ Ammoniata.*—Contains 2 p.c. w/v of quinine sulphate and 1 p.c. w/v of ammonia, or $1\frac{1}{3}$ gr. in 60 ms. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**
2. **Syrupus Ferri Phosphatis cum Quinina et Strychnina.** *Syn.—Easton's Syrup.* (*See* p. 208.). **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

QUININAE BISULPHAS

Quinine Bisulphas

Syn.—Quinine Acid Sulphate.

Source.—Bisulphate of an alkaloid, quinine, obtained from the bark of various species of *Cinchona.*

Characters.—Colourless, transparent or opaque, small needles. Odourless; taste, bitter. Becomes yellow when exposed to light. *Soluble* in 10 parts of water, in 23 parts of alcohol (90 p.c.). Solution strongly acid to litmus.

B. P. Dose.—1 to 10 grs. or 0.06 to 0.6 grm.

QUININAE ET AETHYLIS CARBONAS

Quinine Ethyl Carbonate

Syn.—Euquinine. Tasteless Quinine.

Source.—Prepared by the action of ethyl chlorocarbonate on quinine.

Composition.—Fine, soft, white, matted needles; odourless; almost tasteless. Darkens on exposure to light. Slightly *soluble* in water, soluble in 2 parts of alcohol (90 p.c.), readily in dilute acids.

B.P. Dose.—$1\frac{1}{2}$ to 15 grs. or 0.1 to 1 grm.

QUININAE TANNAS

Quinine Tannate

Source.—A compound of tannic acid with an alkaloid, quinine, obtained from the bark of various species of *Cinchona.* Contains not less than 30 p.c. not more than 35 p.c. of anhydrous quinine.

Characters.—A pale-yellow, or yellowish-white, amorphous powder; taste, slightly bitter, astringent. Slightly *soluble* in water, soluble in alcohol (90 p. c.).

B.P. Dose.—$1\frac{1}{2}$ to 15 grs. or 0.1 to 1 grm.

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Non-official Preparations and Derivatives of Quinine

1. **Quinina, U.S.P.**—An alkaloid obtained from the bark of various species of cinchona. In white micro-crystalline powder, odourless with a bitter taste. An alcoholic solution (1 in 10) is lævorotatory and alkaline to litmus. Insoluble in water. *Dose, U.S.P.*—0.1 grm. or 1½ grs. as a tonic; at least 1 grm. or 15 grs. daily as antimalarial.

2. **Quininæ Glycerophosphas.**—Two kinds, *viz.*, basic and neutral. In obstinate *neuralgia*, or *chronic malaria*. *Dose.*—1 to 10 grs. or 0.06 to 0.6 grm.

3. **Quininæ Hydrobromidum.**—In white acicular crystals soluble 1 in 40 of water. With excess of diluted hydrobromic acid it lessens cinchonism. *Dose.*—1 to 10 grs, or 0·06 to 0·6 grm.

4. **Quininæ Hydrobromidum Acidum.**—Yellowish crystals, very soluble in water. Used hypodermically. *Dose.*—½ to 2 grs. or 0.03 to 0.12 grm.

5. **Quininæ Urethane** (Hydrochloride).—Obtained by heating quinine hydrochloride 3; urethane 15; water 3. Used hypodermically and is non-irritant. In the *injection treatment of varicose veins* it is the method of choice. *Dose.*—½ to 3 grs. or 0.03 to 0.2 grm.

6. **Quininæ Lactas.**—A granular white amorphous powder soluble in water. Suitable for internal and hypodermic use. *Dose.*—1 to 5 grs. or 0.06 to 0.3 grm.

7. **Quininæ Salicylas.**—Silky crystals, sparingly soluble in water. In *remittent fever, rheumatism, neuralgia, and diarrhœa*. *Dose.*—2 to 6 grs. or 0.12 to 0.4 grm.

8. **Quininæ Acetylsalicylas.** *Syn.—Quinine Salacetate.*—In white crystalline powder, 64 p.c. of quinine. *Dose.*—1 to 5 grs. or 0.06 to 0.3 grm.

9. **Quininæ Valerianas.**—In *nervous headache* and *hysteria*. *Dose.*—1 to 3 grs. or 0.06 to 0.2 grm.

10. **Warburg's Tincture.** *Syn.—Tinctura Antiperiodica, B.P.C.*—Take in grains, Aloes 240, Rhubarb 80, Angelica Fruit 80, Elecampane Root 40, Saffron 40, Fennel 40, Chalk 40, Gentian 20, Zedoary 20, Cubeb 20, Myrrh 20, Agaric 20, Opium 2½, Black Pepper 4½, Cinnamon 8, Ginger 8, Alcohol (60 p.c.) *q.s.* Macerate for seven days in one pint of alcohol, press, filter and dissolve in the product Quinine Sulphate 175 grs., Camphor 20 grs. After three days filter and add Alcohol *q.s.* to one pint. *Dose.*—1 to 4 drs. or 4 to 15 mils.

11. **Aristochin.** *Syn.—Aristoquinine.*—The neutral carbonic ester of quinine in white tasteless powder containing 96 p.c. of quinine. Insoluble in water. *Dose.*—1 to 10 grs. or 0.06 to 0.6 grm.

Pharmacology of Quinine Salts

Externally.—The characteristic action of quinine alkaloid is its effect on undifferentiated protoplasm, and it is an active poison to many low forms of vegetable and animal life. Ciliary movements cease and according to Binz a solution of 1 in 20,000 destroys paramecia and amœba. Spermatozoa and ova are destroyed by smaller strengths, and in strengths of 1 in 10,000 spirochæta of vegetable decomposition become motionless, but those of relapsing fever are not influenced by strengths even of 1 in 500.

While the sulphate and hydrochloride have a lethal action on paramecia, there can be no doubt that the newer quinidine and acridine derivatives have a remarkable effect as paramecial poisons and in destroying micro-organisms.

Quinine salts and their derivatives have also a marked anæsthetic action with somewhat prolonged latent period, but the resulting anæsthesia is of longer duration. This anæsthetic action may be possibly due to the effect of quinine on the sensory nerve-endings or to the granular exudate

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formed at the site of injection which presses upon the nerve-endings.

Internally. **Mouth.**—It is a pure vegetable bitter, and has an intensely persistent bitter taste if taken in neutral or slightly acid solution, as the alkaline saliva precipitates the alkaloid. Like other bitters it reflexly stimulates the salivary secretion by exciting the gustatory nerves. The tannate is less bitter and the ethyl carbonate is almost tasteless.

Stomach and intestine.—All the cinchona alkaloids have a marked inhibitory effect on peptic and tryptic digestion. Cinchonine is the most powerful, hence this alkaloid cannot be tolerated for long when taken by the mouth. The monosalts inhibit peptic digestion still further as they use up most of the available free hydrochloric acid to form the more soluble disalts. For this reason only the bisulphate and bihydrochloride should be given when prescribed in the form of tablet by the mouth. Quinine for the most part passes through the stomach unchanged and reaches the duodenum, where the alkaline contents precipitate it as nascent alkaloid which is soluble in bile, and it is only in this form that quinine is absorbed. The absorption is retarded if it is given soon after or with meals. Three things are necessary for its absorption, *viz.* (*a*) solubility in the stomach; (*b*) alkalinity in the duodenum; and (*c*) available bile. The tannate and the ethyl carbonate are absorbed very slowly as they require to be hydrolised by the alkali of the duodenum.

In small doses (1 to 2 grs.) it is a bitter stomachic tonic like calumba, and indirectly it acts as a general and cardiac tonic. In large doses (15 to 40 grs.) it produces the opposite effects—depression and gastro-intestinal irritation.

Blood—In whatever form quinine is given it circulates as quinine base and is present in the plasma, adsorbed on to the surface of the red blood-cells, but not within them. Therefore those parasites that have become intracellular escape from its effect. After ingestion of a single dose of 20 grs. of the sulphate the maximum concentration in the blood is 1 in 150,000; and after a single dose of 10 grs. it is only 1 in 250,000. After absorption into the blood quinine has several specific actions which may best be described under the following heads:—

1. *White corpuscles.*—After small doses of quinine there is some lymphocytosis, possibly due to contraction of the plain muscles of the spleen. After large doses this is followed by a reduction in the number of leucocytes, the lymphocytes being more reduced than the polymorphonuclears. This phase is again followed by leucocytosis, the polynuclear cells being only increased. In animals, not in man, quinine paralyses the movement of the white blood corpuscles. This may be seen by mixing a drop of the solution with a drop of fresh blood under a microscope. If quinine be

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injected into a blood vessel, it at once stops the emigration of the leucocytes; but it has no effect on the amœboid movements of those which have already passed out into the tissues.

2. *Red corpuscles.*—These are not materially affected, though many assert that it increases their number and causes an increase in their size. Hæmolysis occurs only when quinine circulates in the blood in sufficient concentration to cause arrest of the heart, *i.e.*, 0.5 p.c. (Cushny).

3. *Hæmoglobin.*—The oxyhæmoglobin is made a stable compound, consquently the blood cannot either absorb or give up oxygen so readily as in health. Probably this does not occur in medicinal doses.

The malaria parasites.—The causal organisms of malaria belong to the genus *Plasmodium*, which belongs to the class of the protozoa known as sporozoa. Four species are generally recognised as being concerned in the production of human malaria, *viz. Plasmodium vivax*, the parasite of benign tertian malaria; *Plasmodium falciparum*, the parasite of malignant or subtertian malaria; *Plasmodium malariæ*, the parasite of quartan malaria; and *Plasmodium ovale*, a parasite which produces a mild type of tertian malaria in Africa. In all forms of malaria the fever is as a rule quotidian at the beginning of a primary attack, but in the tertian forms it later occurs on alternate days, whilst in quartan it occurs every fourth day, *i.e.* two days intervene between each bout of pyrexia. Quinine in 1 in 10,000 solution inhibits the amœboid movements of the plasmodium *in vitro*. Given by the mouth to infected man the plasmodium shrinks, becomes granular and finally disintegrates. Under quinine the parasites disappear from the peripheral circulation, when as the result of sporulation, the young parasites are set free in the blood plasma. A few of the more resistant type escape and multiply and eventually provoke another paroxysm of fever. It is more effective on the young stages of the asexual parasites which are more susceptible to its effect while they are free in the blood plasma. After the parasites have entered the corpuscles they become resistant to quinine.

Quinine has no effect on sporozoites even in high concentrations, nor has it any action on the crescents and therefore mosquitoes can readily be infected even though the patient may be taking quinine. The exact manner in which it cures malaria is far from settled. In clinical attacks of malaria quinine has little or no action on the parasites until a febrile attack is imminent or has already occurred. The drug has no appreciable effect when given during the incubation period, and has little effect when given on the first or even on the second day of the initial fever. The drug is more effective after the patient has had several paroxysms and the parasites are beginning to decline as a result of

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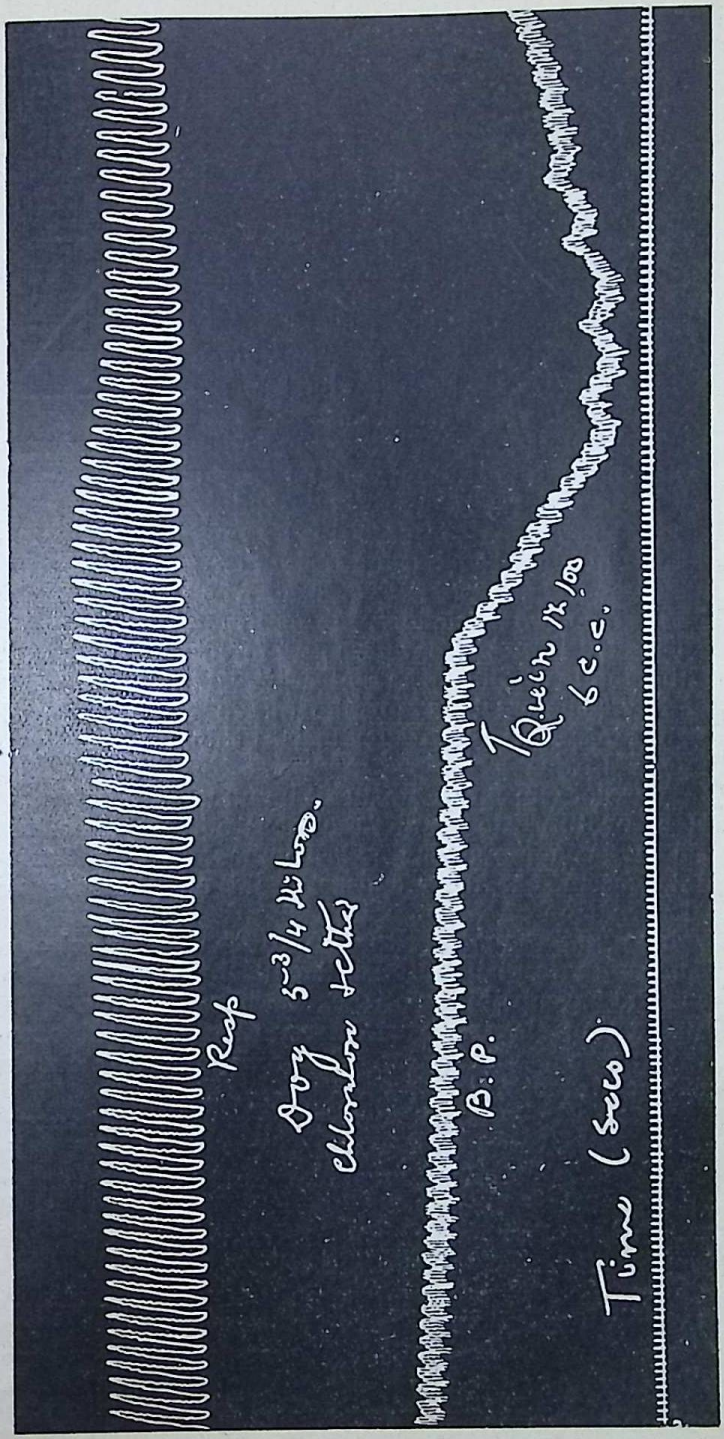

Fig. 12.—Dog. Showing the effect of Quinine on Respiration and Blood-pressure.

At the point of arrow a large dose of quinine, 6 c.c. of 1 p.c. solution was introduced into the femoral vein. Note sudden fall of pressure and weakening and depression of respiratory movements.

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natural defensive mechanism which human beings possess.* Since the drug is rapidly excreted it is difficult to accept any evidence of direct action on the plasmodia. It has therefore been suggested that the action is indirect, and that the effective therapeutic agent may be a metabolite formed by the breakdown of the quinine in the tissue, though no evidence of such a metabolite has been traced. On the other hand Yorke and Macfie maintain that the real action depends upon the capacity of the host to form an immune body in response to the antigen formation resulting from the destruction of a large number of parasites by the medicament. The evidence in favour of the formation of an antibody is however rather meagre. Morgenroth believes that the parasites are unable to enter the red blood corpuscles which are made resistant against penetration.

It is possible that several factors contribute towards the cure of malaria, the one that plays the predominant part is the capacity of the cells of the reticulo-endothelial system to respond to the stimulus of infection by mobilisation, proliferation and functional activation. Administration of quinine merely heightens these responses, and when they are adequate the disease is overcome. The factors such as the direct action of the drug on the parasite and infected red cells, as well as biochemical and other alterations in the serum, help to augment the efficiency of the phagocytic mechanism to varying extent. Krishnan summarises the mode of action of quinine as follows :—†

1. By accelerating the natural immune processes of mobilisation, proliferation and functional activation of the phagocytic large mononuclear cells composing the reticulo-endothelial system, the drug causes rapid engulfment and effective destruction of the parasites.

2. By bringing about an alteration in the electrical condition of parasites and infected red cells by direct action, it increases the susceptibility of these to phagocytosis.

3. By slowing down asexual reproduction and occasionally leading to the formation of sexual forms, it checks the intensity of infection.

4. By indirectly leading to the production of humoral changes (antibodies) and to the sensitisation of the cells of the reticulo-endothelial system it increases the resistance to infection.

5. By causing the removal of effete and old red cells and increasing the output of young red cells it renders the successful entry of parasites into these cells more difficult.

Heart and circulation.—Small doses reflexly stimulate the heart through the stomach, but large doses given intra-

*Quarterly Bulletin of the Health Organisation of the League of Nations, June, 1933.

† Krishnan, Indian Journal of Medical Research, October, 1933.

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venously directly paralyse it; the pulse becomes slow and feeble, and at last the heart stops in diastole. These effects are not observed when quinine is given by the mouth even in large therapeutic doses and are due to direct action of the drug on the cardiac muscle. With weakness of the heart the blood-pressure falls. Intravenous injections cause a sharp and often dangerous fall of blood-pressure. The dextro-rotatory alkaloids of cinchona and quinidine cause greater fall of blood-pressure than their lævorotatory isomerides.

Respiration.—It is not affected by small doses, but is quickened by moderate doses, and in toxic doses it becomes slow and weak and then arrested. The gaseous interchanges are checked.

Liver and spleen.—It has no action on the liver, but contracts the recently enlarged spleen rather by destroying the malarial parasite, and so preventing accumulation of the irritating products—pigments, etc., and reduces the hyperæmia.

Temperature.—Quinine has very little effect upon the temperature in health, but causes a marked reduction in fevers, particularly if they are of malarial origin. It is therefore an antipyretic in malaria. It sometimes lowers the temperature in fevers of non-malarial origin, but the precise mode of its action has not been definitely settled. It was formerly believed that this effect was due to its action on the metabolism. But the amount of quinine which lowers the temperature has no appreciable effect on the metabolism. It is possible that it acts on organisms other than malarial parasites. Its action is like other antipyretic drugs and is due to adjustment of the heat regulating centres, whereby there is increased heat loss from cutaneous vaso-dilatation and lessened heat production (*Hardikar*, 1925 and *Virchow*, 1927).

Metabolism.—Quinine and its derivatives were formerly believed to have a depressant effect on the metabolism. But observations made by Hardikar have failed to show any alteration in the protein metabolism either in man or in animals.

Nervous system—Small doses have a tonic effect upon the nervous system, but large doses produce a train of symptoms known as cinchonism. Frequently there is impairment of the sense of hearing and perhaps of the sight. Ringing in the ears and slight deafness are noticed even after moderate doses. Sometimes there is complete loss of hearing, which disappears in a few days. Dimness of vision and sometimes total blindness may be present, and the patient may become colour blind. It has been thought that the ear symptoms are due to degenerative changes in the spiral ganglia of the cochlea.

The effects on the brain are not uniform. Some complain

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of fullness and heaviness of the head, while in others there is motor excitement with convulsion and delirium. Weakness of the heart and muscles, apathy, impairment of sight and hearing with unconsciousness and failure of respiration are observed in fatal cases.

Injected into animals it causes transient excitement of the central nervous system, but the real effect is depression. The cord is first stimulated and then depressed in mammals. The respiration first becomes quick but subsequently weak and slow (*see* fig. 12), death occurs from respiratory failure. Tremors and convulsion before death are possibly due to asphyxia.

Uterus.—Quinine occasionally acts as an **ecbolic** and it certainly intensifies the labour pains or re-establishes them if they are absent, when parturition has already commenced. Menstruation is sometimes induced by quinine in non-pregnant women. Metrorrhagia is an occasional symptom, although given after labour it often stops hæmorrhage.

Quinine in sufficient concentration causes contraction of uterine muscle in the non-pregnant uterus, *i.e.* after large doses. During pregnancy much depends on the state of the uterus. Large doses (15 to 30 grs.) cause increase in the *intermittent* uterine contractions, and in the presence of weak membranes, open the os and precipitate labour. Larger doses throw the uterus into a state of tonus. In malarial fever there is a greater danger from the fœtus dying as the result of the high temperature caused by the disease. So quinine must be given promptly and immediately, and as long as the doses are sufficiently small (2 to 5 grs. every few hours), and not more than 30 grs. are given during the course of twenty-four hours, there is no danger of ecbolic action of this alkaloid.

Absorption and elimination.—Quinine is absorbed by the duodenum and circulates in the blood as quinine base. Soluble salts are absorbed more quickly, but the rate of absorption varies in different people. Given in solution it appears in the urine very quickly. Quinine however does not circulate in the blood for a long time in any concentration ; after an intravenous injection about 90 p.c. disappears within a minute. Excretion of quinine varies greatly in individuals and day by day. It may be detected in the urine half an hour after administration, and excretion may go on for 48 hours. Probably only about half the quinine administered is excreted by the urine, and according to Ramsden some of it is destroyed by the liver and kidneys. Any that is stored in the body will probably be found in the suprarenal bodies and the spleen, which organs are incapable of destroying it. Administered per rectum absorption is poor, irregular and unreliable, and may irritate the mucous membrane.

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Toleration.—Some persons are very susceptible to the action of this drug. When a small dose produces headache and ringing in the ears, it is due to *idiosyncrasy*. The writer had seen a woman who became collapsed after taking 5 grs. of quinine sulphate.

The role of quinine in the production of black water has not yet been definitely settled. A case of death following the administration of fifteen grains of quinine has recently been reported, the symptoms leading to this result being profuse internal and external hæmorrhage. A case recently occurred when intense urticaria followed the administration of the soluble hydrochloride, later of euquinine, but not of aristochin under which recovery ensued.

Therapeutics

Externally.—Quinine cannot be freely used on account of its cost, though it is a *powerful antiseptic*. A lotion (2 to 4 grs. in 1 oz. of water) has been found very efficacious in diphtheritic conjunctivitis, and as an injection in hay fever, otorrhœa, and chronic cystitis.

Internally.—As an *antiseptic* it may be used as a gargle in stomatitis, diphtheritic ulceration and sore-throat.

As a *stomachic tonic* it is very useful in convalescence from an acute illness, particularly malarial fever. Its efficacy is considerably increased if it is combined with mineral acids and other bitters.

As an *antipyretic* it is far inferior to phenazone, phenacetin, acetanilide or sodium salicylate, but there are many who advocate its use in typhus, typhoid and puerperal fever, acute rheumatism, insolation and pyæmia. It must be given just before the natural defervescence. It is useless in hyperpyrexia.

As an *antipyretic* and *febrifuge* it is considered a specific for **malaria** and all malarial intermittent and remittent affections. A few of them require more than a passing notice :—

(1) *Malaria.*—Quinine acts as a specific in malaria, and a single dose of 10 grs. or two doses of 10 grs. every two or three hours should be given at least two hours before the expected paroxysm. It will then be absorbed into the blood in sufficient concentration before sporulation takes place, and thus will quickly attack the young spores, when they are free in the plasma and before they are able to enter the red blood corpuscles. It is probable that during this stage these asexual parasites are most susceptible to the effect of quinine. Whenever convenient this method should be followed. Sometimes, however, it is not possible to give sufficient quinine before the next paroxysm. In such cases it should be started when the temperature begins to fall so that a total quanitity of 20 to 25 grs. in two or three doses can

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be given before the expected paroxysm. In every case the physician should be guided by the severity of the case, and quinine should be given at once without any reference to temperature in all cases of malignant infection or when there is danger of waiting for the temperature to fall.

Whenever possible quinine should be given after the bowels have been opened, preferably by a dose of calomel and a saline. But this should be regarded as a matter of convenience and not of routine and no time should be lost in giving quinine once the case is diagnosed as of malaria. After the first or second dose, the question of giving a purgative may be considered.

To give large doses of quinine indiscriminately in all cases of malaria is a grave error. In fact relapses are more readily controlled by quinine than are the primary attacks. The treatment requires to be stopped after five to seven days in acute attacks, and if the patient has a recrudescence, then it should be given again for the same period or until the symptoms or the parasites disappear. It should not be used during the period the patient's blood is parasite-free. The tendency in the past had been to give too much quinine and to prolong the period of treatment unnecessarily.

The routine treatment followed by the writer is to give 10 grs. of quinine with $2\frac{1}{2}$ grs. of acid acetylsalicylic in cachets as the first dose when the temperature is beginning to fall, followed by two more doses every three hours; the second and the third doses contain $7\frac{1}{2}$ grs. of quinine instead of 10 grs. If the paroxysm is not checked the treatment is repeated the next day but the second dose should contain 10 grs. of quinine. This usually checks the fever and the same procedure is followed for three to four days after the temperature has become normal. If no more attacks occur the use of quinine should be stopped for at least one week as it is no use giving this drug during the fever-free and parasite-free period. The writer is satisfied with this treatment and rarely had relapses. The success depends upon giving enough quinine, *i.e.*, not less than 20 to 30 grs. within four to six hours, so that it will be absorbed and circulate in the blood in sufficient concentration before the appearance of the expected paroxysm. Besides relieving many unpleasant symptoms and acting as a cholagogue and antipyretic, aspirin helps the action of quinine.

Sinton has pointed out that there exists some similarity between an attack of malaria and an anaphylactic shock, caused by the absorption of foreign protein from the body of the malarial parasite. Alkalies and magnesium sulphate given along with quinine treatment relieve the condition. He believes that the alkali has a catalytic effect on the action of quinine on the plasmodium and helps to lower the hydrogen-ion-concentration of the blood. The method of

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treatment is as follows: On the first day 3 grs. of calomel and 1 oz. of magnesium sulphate are given; on the following day 1 dr. of sodium bicarbonate and 40 grs. of sodium citrate dissolved in 1 oz. of water is given for three doses every two hours: followed after half an hour by 10 grs. of quinine sulphate, 20 grs. of citric acid and 1 dr. of magnesium sulphate in 1 oz. of water. By this method 1 to 3 drs. of quinine can be given within a week. Sinton claims that this method of treatment yields much better results than when quinine is given without an alkali.

The oral administration is the simplest and most practicable and should be the method of choice. The intramuscular method is rarely required unless there is vomiting and other contra-indications to oral use or when oral route is not attended with any success. In any case not more than two injections need be given. In fact Fletcher has shown that after intramuscular injection quinine is absorbed less rapidly than after oral administration; moreover, it does not maintain an effective concentration of quinine in the body for a longer period than when it is given orally. The intramuscular injections are given indiscriminately, and often in cases where quinine is not indicated. This method is painful and may be followed by severe necrosis. The danger, however, appears to have been exaggerated. The intravenous route should be used only in pernicious cases and when immediate action is essential, as for instance in cerebral malaria. The bihydrochloride in 10 gr. doses dissolved in 10 c.c. of distilled water should be used, and the injection made very slowly so that it will reach the heart in low concentration; at least three minutes should be spent over the operation. Where the blood-pressure is low it is always wise to add 2 to 3 drops of 1 in 1000 adrenaline solution to prevent further and possibly a fatal fall in the pressure.

(2) *Enlargement of the spleen.*—With the cure of malaria the size of the spleen is reduced, but the efficacy of quinine is greatly augmented if it is given with iron as in the following prescription:—Quin. Sulph. 2 grs., Ferri Sulph. $2\frac{1}{2}$ gr., Pulv. Rhei 5 grs., Pulv. Ipecac. $\frac{1}{6}$ gr., Pulv. Zingib. $2\frac{1}{2}$ grs., and Sod. Bicarb. $2\frac{1}{2}$ grs., M., T.D. In a recently enlarged spleen, with or without ague, this formula may be used with marked success.

(3) *Malignant form of malarial fever.*—Many deaths occur from this type of fever from want of courage on the part of the physician to administer quinine in sufficiently large doses. From the beginning without any reference to temperature or local symptoms, with stimulants if necessary, quinine should be given. Although it is well recognised that malignant malaria reacts quickly to quinine, it has been found that certain strains of this parasite in special localities are resistant to it, which can be successfully treated by atebrin

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(*see* page 444). Cases of malignant tertian malaria associated with persistent vomiting or threatened coma, should be treated with intravenous quinine, a suitable dose being 0.6 grm. dissolved in 5 to 10 c.c. of physiological saline.

In the *so-called malarial cachexias*, especially those of *the hæmorrhagic type*, quinine is of questionable value. Quinine base has *no hæmolytic action*. If the effect in "black water fever" is real it must be due either to (i) decomposition product of quinine, or (ii) aiding the formation of hæmolysin.

(4) *Intermittent* or *remittent neuralgias* of malarial or non-malarial origin, often yield to quinine.

As regards *prevention of infection*, there is no evidence that the use of quinine is of any effect. But the term "prophylaxis" in relation to malaria is frequently employed to mean the prevention of clinical symptoms following infection and for this purpose it undoubtedly has its uses. Quinine prophylaxis in this sense has proved of great benefit in the case of prisoners in jails and when given to troops serving in malarious countries, and it has been found that the systematic quininisation of school children greatly reduces the spleen rate. In the case of threatened epidemic of malaria the prophylactic use of quinine will save many lives, whilst in any malarious community it will have good effect by reducing the number of human carriers of benign tertian malaria, though it has no effect on the gametocytes of malignant tertian (crescents). It is particularly necessary that the quinine should be administered to children, who form the principal reservoir of the disease. The most effective dose for prophylactic purposes is 10 grs. daily, but it is seldom possible to do this and it is more usual to give 10 to 15 grs. twice weekly. The drug is best given in solution, but it is frequently impossible to give it in this way on a large scale. If tablets are used, the form of the salt used should be the bihydrochloride, these should be fresh and their solubility tested before use.

As an *ecbolic* it is prescribed in uterine inertia during labour, if there is no obstruction. Ten grains followed by a similar dose after one or two hours often strengthen weak pains. It may be used in small doses in amenorrhœa to stimulate menstrual flow.

As a *nervine tonic* it has been used with great benefit in a host of nervous diseases, generally in combination with iron and strychnine, as Easton's syrup.

Quinine in pregnancy.—Much confusion appears to exist regarding the use of quinine in this condition because of its ecbolic effect. As has been pointed out, there is more danger of abortion in an untreated case of malaria than when properly treated with quinine. Quinine should therefore be given irrespective of pregnancy and the patient

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carefully watched. In any case the dose should not be more than 5 grs. at a time and this dose will rarely excite uterine contraction. In patients with a sensitive uterus, or if there be any history of previous abortion or miscarriage, it should be combined with or followed by either potassium bromide, or, according to the urgency of the case, with a preparation of opium. In case of doubt use atebrin.

Other diseases.—In combination with urethane quinine is largely used in the injection treatment of **varicose veins.** The method is to insert the needle of the syringe into the lowest segment of the vein after the part has been cleaned, and to inject slowly after a little blood being allowed to flow into the needle. Keep the needle for 30 seconds, then withdraw and seal the puncture with collodion and wool, or strap it. The solution used is quinine hydrochloride 4 G., urethane 2 G., water 30 c.c. The initial dose is ½ c.c. increased to 2 to 3 c.c. Pregnancy, diseases of the heart with failing compensation and renal disease are contra-indications.

Untoward effects.—Quinine sometimes gives rise to certain unpleasant symptoms, *viz.*, ringing in the ears with impaired hearing and vertigo; irritation of the bladder with frequent urination, common in old persons; hæmoglobinuria; contraction of the uterus and abortion in pregnant women; vomiting; itching, sometimes erythematous, papular or urticarial rash (these often appear after small doses and are due to idiosyncrasy); rarely profound collapse.

Caution.—Quinine should be avoided, or given very cautiously, in acute or subacute diseases of the middle ear, gastro-enteritis, extreme anæmia, active cerebral congestion, skin eruptions, such as erythema, urticaria, etc., and to persons particularly susceptible to its influence.

Prescribing hints.—The routine method of giving quinine is by the mouth and preferably in solution. Plain tablets are absorbed easily unless they are made with a menstruum which may interfere with their solubility in the stomach. Mineral acids (1 m. to each grain) and solution of ferric chloride dissolve the sulphate, but unless an excess of acid is used, it will leave a persistently bitter after-taste. To avoid this it may well be given in an effervescing form dissolved in citric acid, or simply suspended in water. To diminish cinchonism the sulphate may be dissolved by the aid of dilute hydrobromic acid in the proportion of 2 ms. of the acid for each grain of quinine. Too large doses of hydrobromic acid, however, are apt to cause diarrhœa. The after-taste of quinine is soon removed or not perceived at all if the patient swallows a little water after taking the drug, and chews a few bits of betel-nut, myrobalan (*haritaki*), unripe guava, or any other substance containing tannin. For children relatively large doses are required, and they

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tolerate quinine better. Quinine ethylcarbonate and aristochin being tasteless should be preferred.

Quinine is incompatible with the usual alkaloidal precipitants. The sulphate is sparingly soluble in water and requires a dilute mineral acid for its solution. With vegetable astringents it forms an insoluble tannate of quinine. When diluted with water the ammoniated solution forms a precipitate. Precipitate also tends to form with a solution of arsenate, arsenite, phosphate, citrate, tartrate, benzoate, or salicylate, as the resulting compounds are very sparingly soluble in water. With salicylate of soda, quinine forms an ugly looking mass (salicylate of quinine) which requires an addition of some mucilage.

If there is much *gastric irritability*, intramuscular injection may be given first, followed by the bi-salt by mouth. The intravenous injection should be resorted to only in cases of extreme urgency. It should be the method of choice in cerebral malaria. The antiperiodic virtue of quinine is greatly enhanced if combined with aspirin, because of the secretion of bile which has a great solvent action on quinine. In many obstinate malarial fevers, Warburg's tincture may be employed with great benefit, but it should be used with caution, as it causes copious perspiration, fall of temperature and weakness and slowing of the heart. Totaquina may be administered in the form of powder, cachet, pill or in solution with an acid. As it contains all the cinchona alkaloids it is of great value in benign tertian infection, where it acts better than quinine.

The strictest asepsis must be maintained when giving a hypodermic injection of quinine. Several cases are on record where tetanus followed from want of proper knowledge, *viz.*—

(1) Using distilled water as sterile water.

(2) not perceiving that altitude lowers boiling point of water, and

(3) that quinine itself in the powder form may contain these spores. Boiling should not be used, as quinine is altered to quinotoxine in an acid solution. Hence sterilisation under filtration is the proper method.

QUINIDINAE SULPHAS

Quinidine Sulphate

Source.—The sulphate of an alkaloid, quinidine, obtained from the bark of various species of Cinchona.

Characters.—Colourless, needle-like crystals; taste, very bitter. Darkens on exposure to light. *Soluble* in 90 parts of water, and in 10 parts of alcohol (90 p.c.). An aqueous solution is neutral, or weakly alkaline to litmus.

B.P. Dose.—3 to 10 grs. or 0.2 to 0.6 grm.

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PHARMACOLOGY AND THERAPEUTICS

Quinidine was brought to the notice of the profession by Acton as the best remedy in the treatment of **benign tertian** infection. It should be given in 10 gr. doses twice a day for six weeks to two months. The usual method of administration is by the mouth. Intramuscular injection is resorted to only in cases where vomiting is a prominent symptom, or when absorption by the stomach is deficient.

Heart.—Since the introduction of quinidine in the treatment of malaria, its use has been extended to cases of **auricular fibrillation,** specially when there is no cardiac enlargement or valvular disease. In about 50 p.c. of cases it restores the normal rhythm of the heart, but the best results are obtained in cases of recent origin and where the symptoms increase with the onset of fibrillation. It is sometimes useful in **auricular flutter,** the normal rhythm being restored without the intermediate stage of fibrillation. In a majority of cases relapse takes place which requires further use of the drug, but this produces no further beneficial effect. It acts by depressing the cardiac muscle which is more marked in the auricle than in the ventricle so that by reducing the conductivity it lengthens the refractory period by 50 p.c. or more and stops the circus movement. It also reduces the frequency of auricular contraction by reducing the excitability of the auricular muscle and thus stops extrasystole, and inducing normal rhythm benefits tachycardia. Its action differs from digitalis where the effect is due to production of partial block in the auriculo-ventricular bundle thus protecting the ventricles from the innumerable impulses from the auricle.

It is rapidly eliminated, the maximum effect being attained in two hours which disappears after twenty-four hours.

The administration of quinidine is not entirely devoid of danger and sudden death during treatment has been recorded, and is possibly due to failure of the ventricular muscle. It frequently causes distressing symptoms, such as headache, nausea, vomiting, diarrhœa, abdominal pain, giddiness, faintness, buzzing in the ears, general distress, a sense of apprehension, palpitation, præcordial pain, excessive ventricular rate, orthopnœa, sweating, toxic erythema, and urticaria. There may be marked idiosyncrasy when it becomes impossible to push the drug, although it is rather rare when the sensitiveness is so marked as to make treatment impossible. Slight degree of sensitiveness should not prevent a reasonable trial.

According to Hay cases unsuitable for quinidine are :—

1. Badly damaged hearts with old-standing valvular disease, and more particularly when there is failure of compensation with venous engorgement ; here digitalis is the best drug to use.

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2. In patients who suffered severely from angina pectoris, the onset of fibrillation is followed by the cessation of the anginal pain, and it is a question whether one should attempt to restore the normal rhythm.

3. Where there is idiosyncrasy for the drug.

4. Infective endocarditis.

5. Cases with a history of embolism.

Cases suitable for quinidine :—

1. When the fibrillation is of recent origin, and when there is not much dilatation of the heart and no valvular disease.

2. Where the fibrillation is due to, or associated with, an acute infection.

3. When the onset of distress definitely dates from the inception of fibrillation, and it is clear that the abnormal rhythm is the disabling factor.

4. When the fibrillation is associated with exophthalmic goitre, specially where partial thyroidectomy has been performed and the fibrillation persists.

Prescribing hints.—It is usually given in powders, cachets or in capsules in 6 gr. doses three times a day. But it is better to determine the patient's idiosyncrasy to the drug by giving an initial dose of 3 grs. The treatment should be continued for one week and if the normal rhythm is not restored during the period, the chances are that quinidine will not prove successful. With each dose the pulse should be taken, and the use of the drug should be discontinued at least temporarily if the pulse is found to be regular. The total daily dose should not exceed 45 grs. Hay recommends that the daily dose should be given in ten equal doses, every two hours, as its action soon passes off.

ETHYLHYDROCUPREINE HYDROCHLORIDE

Optochin Hydrochloride. (Not official)

An artificial alkaloid closely related to quinine. A whitish amorphous powder with a bitter taste. *Cupreine,* is an alkaloid obtained from *Remijia (Cuprea Bark).*

Dose.—3 to 4 grs. or 0·2 to 0.25 grm.

Uses.—Its actions are similar to quinine, but it has a specific bactericidal action on *pneumococcus.* In dilutions of 1 in 1,000,000 it prevents and in 1 in 40,000 kills the growth of these organisms. It has been successfully used in experimental pneumonia of mice, but has not proved a success in man owing to its untoward effect on the eye even when used in therapeutic doses. Effective doses are unsafe. It is however largely used in ophthalmic practice either in the form of lotion (1 to 2 p.c.), or as ointment, in *corneal ulcers (ulcus corneæ serpens), gonorrhœal conjunctivitis, scrofular ophthalmia* and *keratitis.*

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PLASMOQUINE

$C_{19}H_{29}ON_3$ (*Not official*)

Syn.—Plasmochin.

Source and characters.—A tasteless brilliant yellow granular powder. Soluble in alcohol and water up to 0.03 p.c. at 20°C. A synthetic preparation of quinoline ring. It is *n-diethylamino-isopentyl N-8-amino-6-methoxyl chinolin.*

Dose.—0.02 grm. or 1/3 gr. three or four times a day.

Action and Uses

This synthetic product has been introduced recently as a remedy for malaria, and has been extensively used in almost all parts of the world and has been found effective in benign tertian and quartan malaria destroying all forms of *P. vivax* and *P. malariæ* in doses of 0.06 grm. (1 gr.) to 0.1 grm. (1½ gr.) daily. The therapeutic effects of curing primary attacks of these two types of malaria are about equal to that of quinine, but for curing malignant tertian fever its effect is not so good. Moreover, when used in the above mentioned doses the toxic symptoms often appear. Although it has no effect on the asexual (fever-producing) stages of the malignant tertian parasite, and the parasites multiply unchecked, it possesses the power of destroying the gametocytes of *P. falciparum* in the peripheral blood. This action makes this remedy of great value as a prophylactic, as it prevents the development of the *crescents* in the mosquito host; and for this purpose very small doses are required. Manson-Bahr has shown that a single dose of 0.03 grm. (½ gr.) though not sufficient to destroy the crescents was sufficient to prevent the exflagellation on a glass slide. It has however been found that a dose of 0.02 grm. (⅓ gr.) was sufficient to render the patient non-infective to mosquitoes.

For routine treatment of acute attacks the dose should not exceed 0.02 grm. daily and it has been a common practice to use it in combination with quinine. But in these small doses it has little or no curative effect on the asexual (fever-producing) stages of the parasite, and its use cannot be justified in the acute stage of a primary attack. It was however thought that small doses given daily in the acute stage might prevent the development of the sexual forms of the parasite, which appear as a rule on the seventh day of the primary attack. But it has been found that the onset of crescents in the peripheral blood is not prevented or retarded even by larger doses. Its use should therefore be deferred until the acute stage of the disease has been overcome by either quinine or atebrin.

A mass treatment with small doses of plasmochin, has been employed in many places as an *antimalarial measure*, but the success depends upon the extent to which the group is under control, and Schulemann has expressed the opinion that anti-mosquito measures will be necessary, for though the drug will render the gametocyte carrier incapable of infecting mosquitoes, it will be almost impossible to treat every carrier in a particular place. Combined with anti-larval measures it has given remarkable results in many tea states in Southern India. but this treatment alone will be hopeless in an uncontrolled civil population.

Toxic action.—The symptoms may arise with startling suddenness, but as a rule they are less abrupt. Cyanosis, fatigue, profuse perspiration, and cardiac troubles accompained by attacks of vertigo and fainting are often seen. If it is continued, cyanosis spreads, the temperature rises, and an attack resembling black-water fever develops accompanied by destruction of red-blood cells, hæmolytic jaundice and black urine containing methæmoglobin. Even in this stage recovery takes place if the drug is stopped and the patient properly treated with injections of glucose and adrenaline. As a rule the symptoms of poisoning appear in those whose liver is already damaged, but some patients are specially susceptible to it.

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ATEBRIN

Not Official

It is a dihydrochloride of an alkalimino-acridine derivative. In yellow powder with a bitter taste. Soluble in water forming like quinine fluorescence under ultra-violet radiation.

Dose.—0.1 grm. (1½ grs.) or one tablet, three times a day for five days.

Action and Uses

Its effect on human malaria resembles that of quinine, *i.e.*, it destroys all forms of benign tertian and quartan parasites. Therefore in the treatment of these two varieties of malaria, the choice between them must be decided on other considerations than those of immediate therapeutic efficacy for the clinical cure of a primary attack. Some cases of quartan are resistant to quinine while others are to atebrin. Therefore when one drug fails, the other should be tried. For treating primary attacks of malignant malaria the Malaria Commission of the League of Nations are of opinion that atebrin is very much more effective than quinine, but it has no value on the crescents. Although neither of these complies with the requirements of a *therapia magna sterilisans*, the Malaria Commission believe that it is not wise for general routine use that one of them should be preferred to other. In cases with severe vomiting or other complications which prevent oral administration, atebrin can be given *intravenously* or *intramuscularly*. A suitable dose for intravenous injection is 0.3 grm. (5 grs.) dissolved in 5 c.c. of normal saline. But the best plan is to give one or two intravenous injections of quinine, followed by oral use of atebrin.

The usual method of treatment is to give three tablets daily for five days with a saline purgative in the morning. Sometimes it is given with 0.01 grm. (⅙ gr.) of plasmochin in subtertian malaria to destroy the crescents, but as mentioned before this should be done after the primary attack has been checked, and the two remedies should not be given together.

A valuable property of the drug is to prevent relapses, and it is largely used in chronic relapsing cases. It is a drug of choice when there is idiosyncrasy to quinine and in cases of pregnancy. Although recommended in black-water fever it should be used with caution in view of several recorded cases of methæmoglobinuria.

It is excreted slowly and has been found in the urine even eight or nine days after the expiry of the seven-day course. Its presence in the urine is detected by adding sulphuric acid and heating when a characteristic yellow colour forms, best seen by looking down the test tube.

Toxic action.—Toxicity though low is common when the dose is large. Gastro-intestinal symptoms with severe pain in the abdomen is commonly observed. Yellow staining of the skin with enlarged and tender liver was observed by the writer. Methæmoglobinuria has also been reported. Fatty degeneration of the liver and kidneys in dogs and cats was recorded by DeMello

Class B: Antisyphilitics

HYDRARGYRUM

Mercury

Syn.—Quicksilver.

Source.—A liquid metal obtained from native mercuric sulphide.

Characters.—Silvery-white liquid, easily divisible into globules. Extremely mobile. Boils at 358° C. and solidifies at −39·5° C. *Soluble in nitric acid, and in boiling sulphuric acid.*

B.P. Dose.—½ to 3 grs. or 0·03 to 0·2 grm. *Intramuscularly.*—½ to 1 gr. or 0·03 to 0·06 grm.

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Official Preparations

1. **Injectio Hydrargyri.** *Syn.—Murcurial Cream.*—1 gr. of Hg. in 10 ms. **B.P. Dose.—5 to 10 ms. or 0·3 to 0·6 mil.** (intramuscular).
2. **Hydrargyrum cum Creta.** *Syn.—Grey Powder.*—33 p.c. mercury. A greyish-blue powder. **B.P. Dose.—1 to 5 grs. or 0·06 to 0·3 grm.**
3. **Pilula Hydrargyri.** *Syn.—Blue Pill.*—33 p.c. mercury. **B.P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.**
4. **Unguentum Hydrargyri.** *Syn.—Blue Ointment.*—30 p.c. mercury.
5. **Unguentum Hydrargyri Compositum.** *Syn.—Scott's Ointment or Dressing.*—Contains 12 p.c. mercury.
6. **Unguentum Hydrargyri Nitratis Forte.** *Syn.—Ung. Hydrargyri Nitratis; Citrine Ointment.*—Contains 6.7 p.c. mercury.
7. **Unguentum Hydrargyri Nitratis Dilutum.**—20 p.c. of the strong ointment of mercuric nitrate.

Non-official Preparations

1. **Injectio Hydrargyri Fortis.** *Syn.—Oleum Cinerum*; *Grey Oil.*—Mercury 40, wool fat 26, liquid paraffin 70. *Dose.*—0.06 to 0.12 mil or 1 to 2 ms. intramuscularly every eight days.
2. **Massa Hydrargyri, U. S. P.** *Syn.—Blue Mass; Blue Pill.*—Mercury 33, oleate of mercury 1, glycyrrhiza powder 10, althea powder 15, glycerin 9, honey of rose 32. Contains 32 to 34 p.c. of mercury. *Dose.*—5 grs. or 0.3 grm.
3. **Pilulæ Colchici et Hydrargyri Composita.** *Syn.—Brodie's Gout Pill.*—Dry extract of colchicum, 0.39; mercury pill, 1.04; compound extract of colocynth, 1.04; extract of rhubarb, 1.04; all in grms. for 12 pills; syrup of liquid glucose q.s. *Dose.*—1 to 2 pills.
4. **Pilulæ Digitalis Compositæ, B. P. C.** *Syn.—Guy's Pill; Niemeyer's Pill.*—Powdered digitalis, squill in powder and mercury pill, each 1 gr. and syrup of liquid glucose, *q.s.* *Dose.*—1 to 2 pills.
5. **Pilulæ Hydrargyri cum Creta et Opii, B.P.C.** *Syn.—Hutchinson's Pill.*—Grey powder, 12 gr.; Dover's powder, 12 gr.; compound powder of acacia, 1 gr.; syrup of liquid glucose, *q. s.* for 12 pills. *Dose.*—1 pill.

HYDRARGYRI IODIDUM RUBRUM

Red Mercuric Iodide. HgI_2

Syn.—Biniodide of Mercury. Mercuric Iodide.

Source and characters.—A scarlet-red powder, obtained by the interaction of aqueous solutions of mercuric chloride and potassium iodide. *Solubility.*—Almost insoluble in water, but freely in solution of potassium iodide.

B.P. Dose.—$\frac{1}{32}$ to $\frac{1}{16}$ gr. or 0·002 to 0·004 grm.

Official Preparation

1. **Liquor Arseni et Hydrargyri Iodidi.** *Syn.—Donovan's Solution.*—Contains 1 p.c. of each salt; or ¼ gr. of each salt in 15 ms. **B.P. Dose.—5 to 15 ms. or 0·3 to 1 mil.**

Non-official Preparations

1. **Hydrargyri Iodidum Flavum, U.S.P.**—*Yellow Mercurous Iodide.*—A bright yellow, amorphous powder, contains not less than 99 p.c. of pure HgI. Becomes greenish on exposure to light. Insoluble in water, alcohol and ether. *Dose.*—0·01 gm. or $\frac{1}{6}$ gr.
2. **Hydrargyri Iodidum Viride.** *Syn.—Green Iodide of Mercury*; *Protoiodide of Mercury.*—In greenish yellow, odourless and tasteless powder. Insoluble in alcohol, ether and water. *Dose.*—0.01 to 0.06 gm. or $\frac{1}{6}$ to 1 gr.
3. **Unguentum Hydrargyri Iodidi Rubri, B.P. 1914.**—Mercuric iodide 4 p.c. in benzoinated lard.

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HYDRARGYRUM OLEATUM

Mercuric Oleate

Source and characters.—A light yellowish unctuous substance obtained by triturating yellow mercuric oxide 20 gms., liquid paraffin 5 gms. and oleic acid 75 gms. Heat to 50° C. Contains equivalent of 20 p.c. mercuric oxide.

Official Preparation

1. **Unguentum Hydrargyri Oleati.**—25 p.c.

HYDRARGYRI OXIDUM FLAVUM

Yellow Mercuric Oxide. HgO

Source and characters.—An orange-yellow, amorphous powder; obtained by the interaction of aqueous solution of mercuric chloride and sodium hydroxide. Insoluble in water. Contains not less than 99.3 p.c. of pure mercuric oxide.

Enters into.—Hydrargyrum oleatum, ung. hydrargyri oleati.

Official Preparations

1. **Oculentum Hydrargyri Oxidi.**—1 p.c. mercuric oxide.
2. **Oculentum Atropinæ cum Hydrargyri Oxido.**—Atropine 0.125 p.c.; yellow mercuric oxide 1 p.c.

HYDRARGYRI PERCHLORIDUM

Mercuric Chloride. $HgCl_2$

Syn.—Corrosive Sublimate; Perchloride of Mercury.

Source.—Obtained by the direct combination of Mercury and chlorine. Contains not less than 99.5 p.c. of $HgCl_2$.

Characters.—Heavy, colourless or white, rhombic crystalline masses, or a white crystalline powder. When heated, it fuses to a colourless liquid, which on further heat volatilises as a dense white cloud. *Soluble* in 18 parts of water, in 4 parts of alcohol (90 p.c.), in ether, and in glycerin.

Incompatibles.—Alkalies and their carbonates, potassium iodide, lime water, tartar emetic, silver nitrate, albumen, lead acetate, soaps, and vegetable astringents.

B.P. Dose.—$\frac{1}{32}$ to $\frac{1}{16}$ gr. or 0.002 to 0.004 grm.

Official Preparation

1. **Liquor Hydrargyri Perchloridi.**—$\frac{1}{16}$ gr. in 60 ms. or 0.1 per cent. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

HYDRARGYRI SUBCHLORIDUM

Mercurous Chloride. HgCl

Syn.—Calomel; Hydrargyri Chloridum Mite, U.S.P.; Subchloride of Mercury.

Source.—A salt obtained as a sublimate when a mixture of mercurous sulphate and sodium chloride is heated.

Characters.—A dull white, heavy, nearly, tasteless powder. *Solubility.*—Insoluble in water, alcohol (90 p.c.), or ether. Volatilises when heated.

B.P. Dose.—$\frac{1}{2}$ to 3 grs. or 0.03 to 0.2 grm. Intramuscular injection.—$\frac{1}{2}$ to 1 gr. or 0.03 to 0.06 grm.

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Official Preparations

1. **Lotio Hydrargyri Nigra.** *Syn.—Black Wash.*—0.7 p.c. mercurous chloride.
2. **Injectio Hydrargyri Subchloridi.** *Syn.—Calomel Injection.*—Contains 1 gr. calomel in 20 ms. **B.P. Dose.—10 to 20 ms. or 0.6 to 1.2 mils.**
3. **Unguentum Hydrargyri Subchloridi.** *Syn.—Calomel Ointment.*—20 p.c. calomel.

Non-official Preparations

1. **Pilula Hydrargyri Subchloridi Co.** *Syn.—Plummer's Pill.*—Calomel 12 grs., sulphurated antimony 12 grs., guaiacum resin 24 grs., gum acacia and tragacanth each 3/5 gr., syrup of glucose *q.s.* for 12 pills. *Dose.*—1 to 2 pills.
2. **Pilulæ Hydrargyri Chloridi Mitis Co., U.S.P.** *Syn.—Pilulæ Catharticæ Compositæ.*—Ext. colocynth co., 8; calomel, 6; jalap resin, 2; gamboge, 1.5; all in gms., alcohol diluted *q.s.* for 100 pills. *Dose.*—2 pills.
3. **Unguentum Hydrargyri Subchloridi Compositum, B.P.C.** *Syn.—Calomel Cream*; *Prophylactic Ointment.*—Mercurous chloride, 1 oz.; mercuric oxycyanide, 1 1/4 gr.; wool fat, 1 oz. 175 grs.; yellow soft paraffin, 1 oz.; liquid paraffin, 262 1/2 grs.

HYDRARGYRUM AMMONIATUM

Ammoniated Mercury. NH_2HgCl

Syn.—Ammonio-chloride of Mercury. White Precipitate.

Source.—Obtained by the interaction of ammonia and perchloride of mercury. White, heavy, odourless and tasteless powder. Insoluble in water, alcohol (90 p.c.), and ether.

Official Preparation

1. **Unguentum Hydrargyri Ammoniati.** *Syn.—White Precipitate Ointment.*—5 p.c. ammoniated mercury.

HYDRARGYRI OXYCYANIDUM

Mercuric Oxycyanide

Source.—Prepared by the interaction of mercuric oxide and excess of mercuric cyanide in the presence of water. Contains not less than 20 p.c. and not more than 22 p.c. of HgO, and not less than 77 p.c. and not more than 79 p.c. of $Hg(CN)_2$.

Characters.—A white crystalline powder. *Soluble* in 18 parts of water, solution alkaline to litmus.

B.P. Dose.—1/12 to 1/6 gr. or 0.005 to 0.01 grm. (intramuscular); 0.01 grm. or 1/6 gr. (intravenous).

Additional Non-official Preparations of Mercury

1. **Hydrargyri Benzoas.**—A white crystalline powder. *Dose.*—1/25 to 1/10 gr. For hypodermic injection in solution which should be prepared fresh. Hydrarg. Benzoas 1 grm., Sodium Chloride 1/2 grm., Water 100 grm.
2. **Hydrargyri Succinimidum.**—A soluble preparation used for hypodermic injection. *Dose.*—1/4 to 1/3 gr. Solution generally used is Succinimide 1/4 gr., Cocaine Nitrate 1/5 gr., Aqua 12 ms. *Dose.*—6 to 12 ms. for an injection.
3. **Hydrargyri Lactas.**—Very soluble and non-irritant. Contains 65 p.c. of mercury. *Dose.*—1/8 gr. in 15 ms. of water (hypodermically.)
4. **Hydrargyri Salicylas, U.S.P.**—A white powder slightly soluble in water. Powerful antiseptic and antisyphilitic. For *syphilitic sores*, as ointment or dusting powder. *Dose, U.S.P.*—0.06 gm. or 1 gr. twice a week as injection.

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5. **Hydrargyri Tannas.**—A green tasteless powder decomposed by weak alkalies setting free globules of mercury. Rapidly absorbed from the intestine without the disagreeable symptoms of mercurials, and producing best results in syphilis. *Dose.*—1 to 2 grs. or 0·06 to 0·12 grm. in pill.

6. **Novasurol.** *Syn.—Merbaphen.*—A double salt of sodium mercurichlorphenyl oxylacetate with diethylbarbituric acid. Contains 33.9 p.c. of Hg. Valuable in *portal cirrhosis, ascites,* and *cardiac œdemas,* when it is more effective than digitalis or purin derivatives. In ascites it is generally given in combination with ammonium chloride, the latter being given by the mouth from 5 to 6 grms. daily. Ammonium chloride reduces the alkali reserve in the blood, and helps to produce acidosis. Novasurol is more effective when used after the patient had taken sufficient ammonium chloride to render the urine acid. White crystalline powder, odourless, soluble in water, with slightly alkaline reaction. A powerful *diuretic.* Contra-indicated in acute nephritis and enteritis.

Dose.—As a diuretic or antisyphilitic, 0.5 to 2 c.c. of 10 p.c. solution, intramuscularly or intravenously, once or twice a week.

7. **Salyrgan.**—A complex synthetical mercurial compound. A 10 p.c. solution of a sodium salt of mercury salicylamide-O-acetate Clinically used in *syphilis* and as a *diuretic,* commencing with 0.5 c.c. and then working up to 2 c.c. or 3 c.c. *intravenously, once or twice a week.* In *œdema, ascites* and *pleural effusions.* Best effects are seen in dropsies due to cardiac and cardio-renal disease. Novasurol often causes diarrhœa, but this does not. May be used *intramuscularly* with almost the same results. Diuresis begins after 1 to 4 hours, usually within 6 hours. Best given in the morning. Administration of ammonium chloride 6 grm. daily gives better results. It is relatively non-irritating and gives better results than novasurol. Little or no effect is observed in localised œdemas.

8. **Neptal.**—*Hydroxymercuriproponalamide of orthoacetyloxybenzoic acid.*—Action similar to salyrgan when given by intramuscular injection. Diuresis begins within two hours of administration. In *nephritis* and *œdema* of cardiac and renal origin, and also in *pleural effusion.* Non-toxic. *Dose.*—1 mil or 15 ms. containing 0.035 grm. or ½ gr. of mercury. May be repeated after six days.

9. **Metaphen.**—4-Nitro 3: 5-Bisacetoxymercuri-2-cresol. Contains 59·68 p.c. mercury. Incompatible with acids and alkaloids. Does not precipitate proteins or act on instruments. Used for sterilisation of skin, instruments and hands. More potent than corrosive sublimate. Usual strength is 1 in 5000.

10. **Mercurochrome "220".** *Syn.—Dibromo-hydroxy-mercury Fluorescein.*—In irridescent green scales. Soluble in water. Contains 23 to 24 p.c. of mercury. A non-irritating antiseptic, largely used in *genito-urinary practice* in 1 to 2.5 p.c. solution. Said to be valuable in refractory cases of *cystitis, pyelitis,* etc. Used intravenously acts as a *powerful urinary antiseptic* during excretion. A ½ to 1 p.c. solution as injection in gonorrhœa. A 2 p.c. solution of acetone-alcohol-water mixture has been advocated for sterilisation of the skin before operation. Use has been suggested in *B. coli* infection. 1 p.c. solution in *conjunctivitis, ophthalmia neonatorum* and *blepharitis.* As an internal antiseptic it has been used in *puerperal sepsis, meningitis* and *septicæmia* but the results have been disappointing, the dose being 15 to 20 c.c. of 1 p.c. solution in freshly distilled water. *Dose.*—*Intravenously,* 0.003 to 0·005 grm. per kilo of body weight in 0·5 p c. solution.

Pharmacology of Mercury and its Salts

Externally.—Metallic mercury and its salts are absorbed by the unbroken skin and may be administered either as an inunction or by fumigation. They enter easily through the hair and sebaceous follicles as an oxide or a chloride in combination with the fatty acids of the sebaceous glands. On the denuded or mucous membranes, they produce the following definite actions:—(1) All mercurials are antiseptics and disinfectants, more specially the corrosive sublimate which is one of the most effective of all mercurials, since it dissociates easily and gives the maximum concentration

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of mercuric ions which produce the antiseptic effect. The chloride being soluble in lipoids penetrates into bacteria more easily and is a stronger antiseptic than the sulphate, nitrate and acetate of mercury. In dilutions of 1 in 500,000 the chloride prevents the growth of and in 1 in 25,000 destroys ordinary bacilli. The ammoniate, nitrate, oleate and oxide destroy animal parasites, and are valuable **parasiticides.** (2) Weak solutions of corrosive sublimate ($\frac{1}{2}$ to $\frac{1}{4}$ gr. in 1 oz.), mercurous and many mercuric ointments are antiphlogistic, astringent, stimulant and resolvent. (3) Stronger solutions, as the acid nitrate and the perchloride, cause inflammation and the concentrated ones sloughing.

The usefulness of mercurial salts as germicides is limited. They are precipitated by proteins, they are irritants and have an injurious effect on tissue, and are poisonous when absorbed. It is customary to add some sodium or ammonium chloride to prevent precipitation and to reduce their irritant effect. These form double salts which are less dissociated and therefore less active. Hydrochloric acid and tartaric acid are also used for the same object.

The bactericidal power of mercurials depends upon the concentration used, and whereas they act rapidly in high concentrations, they require longer time in dilute solutions. Thus while corrosive sublimate kills typhoid bacillus with a dilution of 1 in 100,000 in 24 hours, it takes 22 minutes with 1 in 20,000 and $2\frac{1}{2}$ minutes with 1 in 1000. Its action is probably due to adsorption, consequently sufficient time must be allowed to enable the drug to penetrate into the bacteria before they are killed.

Mercury arrests movements of the white blood-corpuscles and prevents suppuration. The ointments reduce swellings and promote absorption of subcutaneous effusions.

Internally. **Gastro-intestinal tract.**—Mercurial salts affect the mouth, gums and salivary glands, causing **salivation** and **stomatitis.** This is not the result of direct local action but takes place during the process of excretion by the salivary glands, for it occurs whether mercury is given by the mouth, subcutaneously or as inunction, and since the saliva contains the metal, it has a metallic taste. The salivation is due to parasympathetic stimulation (Meyer and Gottleib), and is an important and earliest symptom of excessive therapeutic use and of chronic poisoning.

Most of the preparations of mercury pass through the stomach unchanged and produce very little effect here, although taken in large doses, as in cases of acute poisoning, there is congestion and even hæmorrhages. In the intestine they form some compound with albumin. But only a small portion of calomel enters into this combination, as quite a large portion of it can be recovered from the stool in an inorganic form. In the duodenum and upper

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part of the small intestine, insoluble mercury, such as grey powder, blue pill and calomel irritate the intestines to increased peristalsis beginning in the duodenum and extending through the whole length of the gut and diminish the absorption of fluid. As a result of this action the contents are hurried down so rapidly that the bile is not reabsorbed as happens normally, consequently the stools are dark green (calomel motions). X-ray examinations have shown that generally both the small and large intestines are stimulated. Mercurials are therefore **purgatives.** But the soluble preparations, or those salts which become soluble in the stomach, are too irritant to the stomach to be used as such. The stools are usually soft and there is no pain or straining. The purgative action is greatly helped by salines given a few hours later. If the dose is insufficient, or if it fails to produce purgation, or sometimes from idiosyncrasy, mercury may be absorbed producing constitutional symptoms, but is afterwards re-excreted into the bowels as sulphide.

Mercurials are often credited with some disinfectant action in the intestine. They limit decomposition of food, and retard putrefactive changes in the duodenum and intestine, and check flatulence. The disinfectant action, if any, is very slight and possibly is the rusult of the purgative action which removes the decomposing fæcal mass. Large doses may favour bacterial growth by diminishing the intestinal resistance. They have little effect on unorganised ferments of digestion.

Liver.—Mercurials do not increase the amount of bile formed in the liver, although some bile appears in the stool. They aid excretion of bile already formed and are **indirect cholagogues.** The green calomel stools have been ascribed to the antiseptic properties of mercury checking the growth of bacteria in the gut, and so preventing the normal conversion of bile pigments into stercobilin. Since the green colour occurs in the absence of bile, some attribute it to the presence of sulphide. After a brisk mercurial purgative there is improvement of portal circulation and the condition of the liver improves.

Blood and circulation.—Mercury has very little direct effect on the heart and vessels, and the changes observed in the pulse in acute poisoning are really due to shock. In chronic poisoning they are the result of cachexia and malnutrition. Continued long in small doses, mercury not only increases the number of red cells, but increases their hæmoglobin. In this sense it may be considered as a tonic. In large doses it causes anæmia ; but how far these effects are due to the improvement or impairment of digestion, or to the action on the blood itself, is not known.

Kidneys.—Calomel, or sometimes blue pill, in 3 to 5 gr. doses, occasionally acts as a **diuretic,** specially in the

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presence of dropsy. But salyrgan and novasurol are more efficacious than other mercurial salts. They increase glomerular filtration and act on the tubules and diminish the reabsorption of fluids. The best results are seen in cardiac and cardio-renal diseases, and often give better results when digitalis has failed. Diuresis starts within 6 to 8 hours. When purging follows the use of mercurials less diuretic effect is observed. Since mercury is a protoplasmic poison and is concentrated in the kidney, large doses produce acute nephritis and necrosis of the epithelium of the tubules, congestion and acute inflammation of the glomerulus. These effects are more common with soluble preparations than with insoluble salts as they do not accumulate in sufficient concentration in the blood to produce them. Calomel, or blue pill is often used in combination with digitalis and squill in the form of Guy's pill. (*See* pages 258 and 265.).

Absorption and elimination.—Mercurials are freely absorbed from all surfaces, and after absorption they disappear rapidly from the blood and are deposited in the different organs, chiefly the kidneys, the intestinal walls, and the liver, probably in the form of albuminate. From these depots mercury may be mobilised for several months even after the stoppage of the drug. It begins to be excreted within a few hours of its administration, and may last for several days after a single dose. It is excreted chiefly by the kidneys, and also by the cæcum and colon. The organic compounds are eliminated mainly by the kidneys, while the inorganic compounds by the fæces. The elimination is very slow. Therapeutic administration does not as a rule produce an excretion of more than 10 mg. of mercury daily by the kidneys. Whenever the daily excretion is above this, the kidneys suffer injury. The concentration of mercury in the kidneys is higher than in the blood. It is also excreted by the saliva, sweat, milk, gastric juice and bile, but a large portion is reabsorbed from the intestine which makes the quantity excreted in the fæces variable. It has been traced to the fœtus through the placental circulation.

Specific action.—Mercury is specific in syphilis, specially in the primary and secondary stages. This is due to its action as a parasiticide for *Spirochæta pallida*, for mercury in 1 in 20,000 destroys spirochæta in test tubes. It is not possible to estimate the exact amount present in the tissues, but probably it acts in very great dilutions, and is a valuable *chemotherapeutic agent* in the treatment of syphilis. It has no lethal effect on other protozoal infections like malaria or sleeping sickness.

Toleration.—Age, sex, and idiosyncrasy greatly modify the action of mercurials. Children as a rule bear mercury better than adults, and males better than females. Patients

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suffering from granular kidneys, scrofula, scurvy and malarial cachexia are peculiarly susceptible to this drug. Some are very susceptible to it so that a very small dose may cause salivation. Pregnancy is no bar to the administration of mercury.

Acute toxic action.—This is generally due to accidental or suicidal swallowing of tablets or solutions of perchloride, and has been known to follow the retention of strong solution used as uterine or vaginal douches. If a strong solution is taken there is local corrosion of the mouth, œsophagus and stomach with abdominal pain, vomiting purging and the passage of serous or bloody stools; salivation, metallic taste, burning and an ashy discoloration of the mouth and pharynx. Congestion of the stomach and small hæmorrhages, hyperæmia, redness and swelling of the mucous membrane, developing into necrotic surfaces and ulcers along the folds are observed chiefly in the cæcum and colon, the small intestine almost entirely escaping. Mercurial stomatitis develops within 24 hours. The urine becomes albuminous and bloody with casts. Very soon anuria follows with delirium, coma, collapse and death. In a recent case hæmatemesis and melæna with anuria were prominent symptoms before death. Very little effect is observed on the nervous system and the intellect remains clear to the end.

Treatment.—White of several eggs should be given immediately so as to form a non-corrosive albuminate, followed by immediate lavage of the stomach. After this a pint of milk may be introduced into the stomach which may be removed by lavage if vomiting continues. If the stomach permits, early feeds of milk alternating with potassium bitartrate mixture are useful. Sodium hypophosphite, 1 gm; water, 10 c.c. and hydrogen peroxide 5 c.c. per 0.1 gm. of mercuric chloride is more effective (Sollmann). Sodium thiosulphate intravenously has proved of no value. Irrigation of the colon morning and evening is also advisable. This is continued until no mercury is found in the urine on two successive days. The use of alkalies gives the best protection against development of tubal nephritis. If the anuria is not overcome, copious fluid injection may lead to pulmonary œdema.

Chronic toxic action, Hydrargyrism or Mercurialism.—This is now rare, but occurs occasionally either as the result of accident or malpraxis, and among workers in mercury. The first indications of mercurial poisoning are fœtor of the breath and soreness of the gums (the medicinal administration of mercury should not go further) soon followed by a disagreeable metallic taste; swollen, red, spongy gums, bleeding on the least touch; and increased salivary discharge. The appetite disappears, there is a feeling of weight and discomfort in the stomach, with nausea, colicky pain and diarrhœa. Skin eruption often appears even when given by the mouth, though more common when used as inunction. These symptoms increase, the tongue becomes furred and swells, the tonsils and pharyngeal glands enlarge, there is swelling and tenderness of the parotid and submaxillary glands, the teeth get loosened, the gums recede and become ulcerated, the saliva gets thick and viscid, and pours out of the mouth, fever and depression set in. If the dose is large and long continued these symptoms are aggravated, and end in the falling out of the teeth, ulceration and abscess of the mouth, necrosis of the jaw-bones, great prostration, anæmia, emaciation, repeated hæmorrhage, and death.

Protracted exposure to a moderate degree of mercurial vapour produces a different train of symptoms generally known as **mercurial paralysis.** Besides the cachectic symptoms there are muscular tremors, first beginning at the face, then invading the arms and the legs, extreme weakness of the affected muscles; mental weakness,

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and functional disturbance of special sense. These tremors increase by attempts at voluntary movement, *i.e.*, they are "intention tremors.' A condition known as **mercurial erethismus**, is characterised by hyper-irritability, restlessness, timidity or shyness, muscular weaknes, or sleeplessness. Delirium with transitory hallucination may appear.

Metallic mercury vaporises even at the ordinary temperature and may produce poisonous effects even though the evaporating surface be small if the emanations from it continue for any length of time.

Several cases are on record in which mercurial cachexia has resulted from vaporisation of the mercury with which the backs of mirrors are coated.

Therapeutics of Mercury and its Salts

The therapeutic uses of mercury and its salts are fourfold: *externally*, they are (1) antiseptic, (2) antiparasitic; and *internally*, (3) antisyphilitic, and (4) cathartic.

Externally.—As an **antiseptic**, cyanide and perchloride of mercury are used, but the solution of the latter is largely employed for disinfecting purposes, as well as in **surgical** and **obstetric** practice. A solution of oxycyanide 1 in 5,000 to 1 in 10,000 is useful for washing out the bladder and urethra in gonorrhœa, while a lotion of 1 in 5,000 is used in ophthalmic work. As it does not attack metals the lotion can be used for instruments (1 in 200). A lotion of perchloride 1 in 1000 is strong enough for washing infected rooms, furniture, articles, linen, the surgeon's and gynæcologist's hands, the parts to be operated upon, and for moistening dressing, towels, wool, etc. A lotion (1 in 10,000) may be ordinarily used for washing wounds and ulcers, but the former strength can be advantageously employed if they are foul or of syphilitic origin. In obstetric practice a solution of 1 in 5000 is the strength ordinarily used for irrigation of the vagina and uterus, but its strength requires to be diminished to 1 in 10,000 if used continuously for any length of time.

The following are the disadvantages of perchloride of mercury as a disinfectant:—

(1) It is very poisonous to man.

(2) It corrodes metals.

(3) It combines with albumin—forming an albuminate, on which account it is not good for the disinfection of fæces, unless an acid is also present.

As a parasiticide.—Citrine, oleate and white precipitate ointments and perchloride lotion (1 to 2 grs. in 1 oz. of water) are employed to destroy the fungus of tinea, such as of ringworm, mentagra, and favus; and animal parasites, such as the various kinds of lice and their nits, and the *Acarus scabei*. The red oxide or citrine ointment is very effective in tinea ciliaris. The oleate is a useful application in pityriasis versicolor.

As a remedy for pruritus.—Blue ointment, calomel ointment (1 dr. to 1 oz.), and black wash relieve the distressing itching of many skin disease, such as urticaria, prurigo,

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pruritus ani, psoriasis, lichen, pityriasis of the scalp and eczema. If applied with care and not to a large area, there is very little danger of salivation.

As a stimulant and promoter of absorption.—The liniment and the various ointments, such as oleate, red precipitate, Scott's and red iodide are used for dispersing glandular enlargement, as buboes; and for promoting the absorption of inflammatory products, as in chronic joint disease, chronic peritonitis and periostitis. Red iodide of mercury ointment is a good application for **goitre**, especially if the patient be made to sit in the sun or before a fire immediately after the application has been made.

As an antiphlogistic.—Diluted citrine ointment if applied over whitlows and boils and then covered with plaster rapidly causes them to abort. Mercurial ointment is useful in onychia and paronychia. A ten minutes' application followed by a poultice every hour cuts short the inflammation.

As a specific.—Mercurial ointments and black wash are always prescribed for dressing over chancres and other syphilitic sores. Black wash is an unirritating application, when the sores are kept wet with a bit of lint soaked in it. Nothing is so good as to wash all suspicious sores with a perchloride lotion (1 in 500). A cyanide of mercury lotion (5 to 15 grs. in water 1 oz.) is a good local application to syphilitic sores. Besides their use in syphilitic sores, they are of great service in all varieties of skin diseases, originating from syphilis. It should be borne in mind that in all syphilitic sores the local application must be combined with internal administration of anti-syphilitic remedies like bismuth, mercury or arsenic.

Eye.—Mercury is used in certain diseases of the eye, *e.g.* in conjuctivitis, blepharitis and keratitis. For this purpose oculentum hydrarg. oxidi is generally used. Finely powdered calomel is also applied locally in syphilitic and other affections of the eye (phlyctenular ophthalmia). When applied in this way potassium iodide must not be simultaneously administered internally, otherwise it will appear in the lachrymal secretion and then, mixing with the calomel, will produce an iodide of mercury, and violent inflammation of the eye will be the result.

Internally. **Gastro-intestinal tract.**—Local syphilitic sores in the mouth soon heal under the use of the perchloride mouth-wash (perchloride 4 grs., acid. hydroch. dil. 10 ms. in water 10 ozs.). **Vomiting** in infants whether occurring immediately after feeding or at other times is stopped by grey powder in $\frac{1}{12}$ gr. or $\frac{1}{8}$ gr. given every two or three hours. **Infantile diarrhœa** whether acute, subacute or chronic, with clay-coloured, offensive, or dark green, or slimy, or curdy, stools, soon yields to small doses of calomel or grey

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powder. In **infantile cholera**, the vomiting and purging are soon arrested by an hourly dose of grey powder ($\frac{1}{6}$ gr.), while fractional doses of calomel ($\frac{1}{8}$ to $\frac{1}{12}$ gr.) have been found useful in the early treatment of cholera when given every hour till the colour of the stool alters. Cases of obstinate **hiccough** have been checked by small doses of calomel. Blue pill or calomel is given as a **purgative**, but it should not be prescribed to habitual opium-eaters, or to a patient under opium treatment, for fear of absorption and constitutional symptoms. In every case, it is a good plan to follow the mercurial by a saline aperient. Calomel or grey powder in small doses or as a purgative clears the thickly coated creamy tongue of many acute diseases.

In biliousness or hepatic derangement due perhaps to free living, a dose of blue pill or calomel at night, followed by a dose of compound senna mixture, or Seidlitz powder or compound liquorice powder next morning, produces excellent results.

Inflammatory diseases.—Few now prescribe mercury in acute inflammatory diseases, except in iritis, but there are many who yet use it in meningitis and inflammation of the serous membranes in conjunction with iodides.

Dropsy and ascites.—Calomel given several times a day acts as a diuretic in **cardiac dropsy**. Its efficacy is greatly increased if combined with digitalis and squill, as in Guy's pill (*see* page 258). It benefits, though temporarily, **ascites** due to **cirrhosis** of the **liver**. It should not be given in renal dropsy. Recently novasurol and salyrgan are widely used as diuretics in ascites and in cardiac and other dropsies with better results. An initial dose of 0.5 c.c. of a 10 p.c. solution is first given to test the tolerance of the patient. Subsequently 1 to 2 c.c. is given once or twice a week. Salyrgan is less toxic than novasurol, although given intramuscularly may also cause local necrosis.

Syphilis.—All recent investigations tend to establish even more firmly the importance of mercury in the treatment of syphilis, and without underrating the value of the organic arsenical preparations in the treatment of this disease the fact remains that we cannot do without mercury. It is true that in these modern days injections of various salts, soluble and insoluble, have somewhat replaced oral method of administration, as in this absorption is uncertain and there is a great liability to gastro-intestinal disturbance. But if a patient cannot be kept under the close supervision which the treatment by injection or inunction necessitates, then oral administration is of value. Its efficacy is more marked in primary and secondary syphilis, but opinions differ as to its efficacy in tertiary syphilis. The administration should be started as soon as the disease is diagnosed, and it is now recognised that the chances of success are greater

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the earlier the treatment is commenced. By whatever method it is administered mercury tends to produce cumulative effects, therefore in the treatment of syphilis there must be periods of rest when the patient should not get any mercury. It is customary to stop treatment for a month after a period of four to six weeks. During this period the mercury stored in the tissues is gradually liberated and excreted. Mercury is also valuable as a *prophylactic*, for this purpose calomel 33 p.c. with lanoline ; or oxycyanide of mercury 0.66 G., glycerin 50 c.c. and water to 500 c.c., heated in a water bath for 1 hour, may be applied as inunction into the part exposed. To be effective the application should be made within 4 to 5 hours after exposure. But its thorough application by women is impossible. For the treatment of syphilis mercury may be administered by the following methods :—

1. *By the mouth.*—This is by far the most convenient route, but it is rather difficult to administer sufficient mercury on account of its effect on the digestive tract and purgation which causes the absorption to be irregular. The preparations used by this route are innumerable. Blue pill, grey powder, and calomel are generally used, but being insoluble they are liable to bring on diarrhœa, therefore in the routine treatment opium is given with it. Proto-iodide and sublimate are probably the most reliable remedies given internally. Dupuytren's pills are an example of the use of perchloride of mercury, each pill cotains Hydrarg. Perchlor. $\frac{1}{6}$ gr., Ext. Opii $\frac{1}{3}$ gr., Ext. Guaiaci $\frac{2}{3}$ gr. The dose may be gradually raised avoiding salivation and always remembering variation in toleration. The mouth must be kept clean during the treatment. It is better to use the proto-iodide in the early secondary and keep the sublimate for the late secondary and tertiary stages. With the sublimate gastric intolerance is frequent but salivation is not marked, with the proto-iodide gastric intolerance is infrequent but stomatitis is more common.

2. *By the rectum.*—Mercurial suppository is used for local action.

3. *Fumigation.*—Volatilised calomel is administered by this method, simultaneous diaphoresis induced by steam helps its action. It sometimes causes great weakness and prostration. It is not used now a days.

4. *Inunction.*—By rubbing blue ointment, liniment or oleate of mercury into the skin mercury can be rapidly introduced into the blood. The inner surface of the thigh or the axilla is a suitable spot for inunction. This method is specially useful for the treatment of young children ; 20 to 60 grs. of blue ointment may be rubbed in nightly or every other night. The site of rubbing should be varied for fear of local irritation. The German ointment (1 of Hg. in 3) is

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no doubt superior to the B.P. preparation, but much of the success of the treatment of syphilitic cases at Aix is due probably to the superior climate of the place and the regulated life of the patient. The advantage of this method is that digestion is not disturbed, but it is dirty and disagreeable and special skill is required to avoid cutaneous irritation. By this method sufficient can be introduced to produce saturation of the system in about two weeks.

5. *Endermically.*—Calomel is dusted over raw blistered surfaces or ulcers, or mercurial lotion applied. Mercury may thus be absorbed.

6. *Injection.*—This may be *intravenous* or *intramuscular.* Where a very quick effect is desired and in cases where organic arsenical preparations are undesirable the intravenous injection of 1 c.c. of 1 p.c. solution of the perchloride every other day has been suggested, but these tend to produce fibrosis which precludes the use of the vein for future injection, besides the risk of embolism and production of toxic symptoms. Only one-third of the maximum dose tolerated intramuscularly can be given intravenously without producing toxic effects, therefore the dose is less, but since mercury is excreted more rapidly when given by this route these injections require to be repeated more frequently. Oxycyanide is more suitable for intravenous use (gr. $\frac{1}{6}$). But there is no evidence that a sufficient concentration of mercury can be produced in the blood by this route. As regards intramuscular injections the preparations may be *soluble* or *insoluble.* The advantages of the soluble preparations are that being more speedily absorbed their effect is more rapid and the exact quantity absorbed is known. The disadvantage is that rapid absorption means frequent injections either daily or on alternate days. The advantage of the insoluble preparation is that a large dose of mercury is put in, which usually suffices for a week, and that from these "depots" the mercury continues to be absorbed for some weeks. On the other hand the disadvantages are—accuracy of dosage is impossible, toxic symptoms may continue long after suspending treatment by absorption from the above mentioned "depots". The injection is made deep into the gluteal muscle.

Amongst the soluble salts thus injected are the perchloride $\frac{1}{3}$ gr. dissolved in 17 ms. of distilled water, to which a little sodium chloride $\frac{1}{6}$ gr. is added ; or the mercury biniodide or the oxycyanide in strength of $\frac{1}{6}$ gr. The most powerful and undoubtedly the most effective of the insoluble salts is calomel. Formerly "Grey oil." was used, but this has been replaced by Calomel Injection and Mercurial Cream. These possess the following advantages, *viz.* –

(1) They are painless.
(2) They are absorbed slowly and slowly excreted.

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(3) They are less likely to produce stomatitis and gastro-intestinal irritation.

(4) The therapeutic effects are more lasting.

Intraspinal injection of mercurialised serum has been advocated for the treatment of cerebrospinal syphilis. It is prepared by adding 1 c. c. of 0.13 per cent. mercuric chloride to 12 c. c. of normal human or horse serum, heating to 56°C. for one-half hour, when a clear solution is formed. This dose is injected by gravity at body temperature. The cerebrospinal fluid is first withdrawn till its pressure is 30 mm.

Caution.—Unless appetite and digestion are good mercury should not be given by the mouth. Weak, anæmic and scrofulous subjects, and those suffering from kidney disease cannot bear mercurials. For fear of absorption it should not be employed over a large area. Concentrated solutions should not be used as injections into the vagina and uterus.

Prescribing hints.—As a purgative mercury is usually prescribed in the form of either calomel or blue pill. They may with advantage be used at bed time to be followed by a saline, either black draught, Epsom salts, Glauber's salt, or Seidlitz powder. Grey powder in fractional doses is a valuable remedy for children's dyspepsia. For the treatment of syphilis mercury is generally given by the mouth either in solution or in the form of a pill and considerable quantity can be absorbed from insoluble compounds when given by the mouth. Grey powder is generally used in 1 gr. doses. To prevent looseness of the bowels it may usefully be combined with the same quantity of Dover's powder. This combination may be given in the form of pills, powder, or tablets. The administration of mercury should be stopped, or the dose reduced as soon as the patient begins to complain of soreness of the gums. Inunction is best suited for children, and hot baths aid absorption and elimination of mercury. The oxycyanide should not be used with potassium iodide. When mercury is not tolerated by the mouth the best method is the injection, and the official injections may be used for the purpose. Being insoluble they are less painful, and as the absorption is slow the injections are given less frequently, once or twice a week. As a diuretic mercury is given in the form of Guy's pill, or as injections of novasurol or salyrgan.

For external use the oleate is a very useful preparation and is non-irritant. The white precipitate ointment is a valuable antiparasitic and may be used diluted with equal parts of boric ointment. The student should remember that Liquor Hydrargyri Perchlor. is incompatible with alkalies, and when combined with carbonate of ammonia it forms an insoluble precipitate of ammoniated mercury, which is less poisonous and can be dispensed suspended with mucilage and a "Shake the bottle" label used. With potassium iodide it

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forms potassium mercuric iodide. If however the carbonate of ammonia be added after this combination no precipitate of ammoniated mercury is formed. With tannic acid or substances containing it, salts of mercury form insoluble tannates.

BISMUTHI CARBONAS

Bismuth Carbonate

Syn.—Bismuth Oxycarbonate; Bismuth Subcarbonate.

Source—Obtained by the interaction of bismuth nitrate and a soluble carbonate.

Characters—A white or creamy-white powder; odourless and tasteless. *Insoluble* in water, completely soluble with effervescence in nitric and hydrochloric acids.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm.

Official Preparation

1. **Trochiscus Bismuthi Compositus.**—2¼ gr. in each.

BISMUTHI SALICYLAS

Bismuth Salicylate

Syn.—Bismuth Subsalicylate.

Source.—Obtained by the interaction of solutions of bismuth nitrate and sodium salicylate.

Characters.—A white or nearly white, amorphous powder; odourless and tasteless. *Insoluble* in water.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm. By intramuscular injection:—1 to 2 grs. or 0.06 to 0.12 grm.

Official Preparation

1. **Injectio Bismuthi Salicylatis.**—Contains 2 grs. of bismuth salicylate in 20 ms. **B.P. Dose.—10 to 20 ms. or 0·6 to 1.2 mils intramuscularly.**

BISMUTHUM PRAECIPITATUM

Precipitated Bismuth

Source.—Obtained by the reduction of a solution of bismuth trichloride in hydrochloric acid by means of hypophosphorous acid. Contains not less than 98.5 p.c. of metallic bismuth.

Characters.—A dull grey powder. Easily diffusible in water. *Insoluble* in water.

B.P. Dose.—1½ to 3 grs. or 1 to 0.2 grm. intramuscularly.

Official Preparation

1. **Injectio Bismuthi.**—Contains 0.2 grm. in 1 mil; or 3 grs. in 15 ms. **B. P. Dose.—8 to 15 ms. or 0.5 to 1 mil intramuscularly.** This is known under the proprietory name of *Bismostab.*

Non-official Preparations

1. **Pasta Bismuthi et Iodoformi.** *Syn.*—B.I.P.P.—Mix bismuth subnitrate 1, iodoform 2, and stir in liquid paraffin 1 or *q.s.*

2. **Insufflatio Bismuthi et Morphina.** *Syn.—Ferrier's Snuff.*—Bis. Subnitrate 180, Morph. Hydrochlor. 1, Powdered Gum Acacia 60. Mix. Useful in *coryza.* AP inch each time till the nostrils are cleared.

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3. **Pulvis Bismuthi Co., N. H. I.**—Bismuth carb. 1, sod. bicarbonas 1, heavy magnesium carbonate 3, prepared chalk 3. For intensive treatment of gastric and duodenal ulcers. *Dose.*—½ teaspoonful in a little water.

4. **Liquor Bismuthi et Ammonii Citratis, B.P.C.**—Bismuth subnitrate, 70; citric acid, 52; dilute solution of ammonia, *q.s.*; distilled water, *q.s.* 1000. *Dose.*—2 to 4 mils or ½ to 1 dr.

Additional Derivatives of Bismuth

1 **Trepol.**—Tartro-Bismuthate of Potassium and Sodium suspended in oil. Contains about 64 p.c. of active bismuth. Perfectly stable and does not produce any symptoms of toxicity. Mainly used in the primary and secondary stages of *syphilis*. *Dose.*—Intramuscular, 2 c.c. (=0.2 grm. of the compound in oily suspension) every 3 or 4 days until a total of 2.8 or 3 grm. is reached.

2. **Neo-Trepol.**—Contains 90 p.c. of bismuth. Is a suspension of finely divided, precipitated metallic bismuth in isotonic serum. Gives better and quicker results than trepol. Used intramuscularly and the injections are painless. Useful in tertiary stages and in old cases with no apparent lesions but with a positive Wassermann reaction. *Dose.*—1.5 to 2 c.c. every 3 or 4 days.

3. **Muthanol.**—An oily suspension of radio-active bismuth hydroxide. *Dose.*—1st treatment, a series of ten injections followed by 10 days rest, continued till specific lesions disappear or Wassermann reaction becomes nagative. 2 c.c. ampoules contain 0.15 grm. bismuth oxide.

4. **Bismogenol.**—A bismuth salt of oxybenzoic acid, possibly bismuth salicylate. Put up in oily suspension containing 0.5 to 0.06 grm. of bismuth per c.c. Complete course 15 to 20 injections of 1 c.c. given every 3rd day.

5. **Bismuth Arsphenamine Sulphonate.** *Syn.—Bismarsen.*—A yellow soluble, compound. Arsenic 13 p.c. and bismuth 24 p.c. Valuable in early syphilis in 0.1 to 0.2 G. *intramuscularly. Dose.*—0.2 G. in 1 c.c. distilled water to which 2 ms. of 0.2 p.c. solution of butyn has been added. Two injections weekly.

6. **Quinine Bismuth Iodide.** *Syn.—Quinby.*—Contains 20 p.c. of bismuth of variable composition. *Dose.*—3 c.c. of an oily solution.

7. **Bismuth Beta-naphtholate.** *Syn.—Orphol.*—Less irritating than naphthol. A gastro-intestinal antiseptic and astringent. *Dose.*—0.5 gm. or 8 grs.

8. **Bismuth Oxychloride.**—Impalpable non-irritating powder used as a cosmetic and as a sedative coating in irritable conditions of the mouth, throat, vagina, and rectum. *Dose.*—5 to 20 grs or 0·3 to 1·2 grms.

9. **Bismuth Oxyiodogallate.** *Syn.—Airol.*—A greyish-green powder used as a substitute for iodoform, and injected as an emulsion with glycerin (10 p.c.) in *gonorrhœa.*

10. **Bismuth Pyrogallate.** *Syn.—Helcosol.*—A yellow powder soluble in alkaline secretions. Used as an antiseptic in skin diseases. *Dose.*—2 to 8 grs. or 0·12 to 0·5 G.

11. **Bismuth Subgallate, U.S.P.** *Syn.—Dermatol.*—A yellow, odourless, non-irritating and non-poisonous powder, superior to iodoform as a dressing. It may be applied as a paste, powder, collodion or ointment. Found invaluable in *tubercular diarrhœa.* Has been used also in *gastric ulcer* and *cancer. Dose, U.S.P.*—1 gm. or 15 grs.

12. **Bismuthi Subnitras.**—A heavy, white inodorous powder with slightly acid reaction. Insoluble in water. *Dose.*—5 to 20 grs. or 0.3 to 1·2 G.

13. **Bismuth Tannate.**—A yellow powder, insoluble in water. Useful in *diarrhœa* and *dysentery. Dose.*—5 to 30 grs. or 0.3 to 2 G.

14. **Bismuthi Tribromophenas.** *Syn.—Xeroform.*—A greenish-yellow powder. Powerful intestinal antiseptic, recommended in *cholera.* Used also as a dusting powder in place of iodoform. *Dose.*—5 to 15 grs. or 0·3 to 1 G.

Pharmacology of Bismuth Salts

Externally.—Bismuth salts have no action on the unbroken skin, but applied to wounds they dry the secretion and form a protective covering and help healing. The

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action is purely mechanical. On the denuded surface they act as sedative, mild astringent and antiseptic.

Internally. **Gastro-intestinal tract.**—Bismuth salts blacken the tongue, have no taste and produce a feeling of roughness in the mouth. In large doses they act as direct **sedative** to the mucous membrane of the stomach and intestine. They act physically by shielding the nerve-terminations from the irritating secretions, by forming an adhesive coating on the wall of the stomach and intestines, and so protect them from the irritation of food and secretions. As a consequence of this sedative effect, they act as antiemetics and mild astringents. They also control fermentation, especially the salicylate, naphtholate, etc., and are therefore intestinal antiseptics. Bismuth subnitrate splits up into bismuth oxide and nitric acid in water, liberating nitrous fumes which tend to contribute toward the antiseptic property of the drug. It passes out with the fæces as a sulphide, colouring them leaden black.

Absorption and elimination.—The rate of absorption when given intramuscularly depends upon the site of injection and on the nature of the preparation used. The exact manner in which it is absorbed is not known, although it is possible that the phagocytic cells may play some important part in this process. The rate of absorption is slow and varies with the dose, and the number and frequency of injection. Beinhauer and Jacob made a study of absorption by the X-ray examination, and found that iodo-bismuth of quinine was absorbed readily, neo-trepol less so, and potassium bismuth tartrate was not absorbed after 12 days. The solubility of the preparation used is an important factor in the process of absorption. Insoluble compounds slowly become soluble by the interaction with the proteins, so that most of the compounds are tissue-soluble. Oily suspensions delay these tissue reactions and become encapsulated before they are absorbed, while the water-soluble ones are precipitated and react like insoluble compounds. After intramuscular injection some may be stored in the liver and other organs, but the greater portion is eliminated by the kidneys, liver and the intestine. Minute quantities have been traced to saliva, tears and sweat. It appears in the urine within 18 to 24 hours, and can be detected even after 20 to 30 days. Traces have been found in the cerebro-spinal fluid after 0.2 gm. of trepol.

Kidneys.—Stockton* claims that Bismuth Sodium Tartrate given intramuscularly acts as a powerful **diuretic.** It is in many respects superior to mercurial diuretics, being safe and effective. Its action is less sudden but more prolonged, and acts by mobilising salt in the tissues of the body and bringing it into the blood stream. The usual dose is 0.3 grm.

* *Archives of Internal Medicine* (1932, 1, 142).

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Toxic effects.—The earliest symptoms are a disagreeable taste, coated tongue, foul breath and a blue line along the margin of the gums. These are followed by loss of appetite, nausea, vomiting and diarrhœa with stomatitis, nephritis and enteritis. Occipital headache, restlessness, mental depression and tingling of the hands followed the use of a certain number of injections of bismogenol (basic bismuth salicylate). The urine contains albumin and casts. Weakness, slowness and inco-ordinate movements follow and may lead to tetanic convulsion. There may be complete paralysis and death. In severe forms of ulcerations of the mouth, cancrum oris may supervene.

Attention to oral hygiene and administration of sodium thiosulphate control gingivitis and stomatitis which are most troublesome. Sometimes serious exfoliative dermatitis and rarely jaundice may appear.

Administration of large doses of subnitrate for radiological purposes gives rise to symptoms of poisoning due to the formation of nitrite in the large intestine by the reducing action of putrefactive fæcal bacteria. The symptoms are methæmoglobinuria, cyanosis, diarrhœa, asphyxia and death from respiratory failure.

Resnik (*Bull. John Hopkins Hospital, May.* 1926) reports a case of bismuth poisoning following the use in a fortnight of 5 to 7 oz. of subnitrate. The chief symptoms were a bluish black discoloration of the gums, which were swollen and inflamed; a similar discoloration of the tongue, most marked at the apex of the papillæ; a patchy, diffuse discoloration of the buccal mucosa; swelling and tenderness of the gland; moderate anæmia and basophilic stippling of the red cells, clinical picture closely resembling lead poisoning. Bismuth was detected in the urine. Recovery followed the withdrawal of the salt.

Therapeutics of Bismuth Salts

Externally.—Bismuth is a **cosmetic**, the oxychloride being preferred for this purpose, as it can be reduced to the finest powder. As a local sedative, astringent and antiseptic bismuth may be applied in the form of powder, lotion or ointment to chapped hands and nipples, irritable ulcers, intertrigo, herpes, eczema, etc. Bismuth salicylate, dermatol and many non-official derivatives may be used as substitutes for iodoform. Bismuth has been used as a bismuth-iodoform-paste (B.I.P.P.) in the treatment of tubercular sinuses, and fistulæ. It is injected into these and very good results have been obtained. The chief disadvantage is that both bismuth and iodoform may be absorbed and produce toxic symptoms, but the relative nontoxicity is due to the presence of paraffin which prevents their absorption. Ferrier's snuff checks coryza and chronic nasal catarrh.

Internally.—As a *gastric sedative* bismuth salts are remarkably efficacious in all irritable and painful gastric disorders, such as catarrh, vomiting, indigestion, gastrodynia

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pyrosis and ulcers, simple and malignant. The only drawback to their use is that they cause constipation. The carbonate is generally combined with magnesium carbonate and bicarbonate of soda as in Pulvis Bismuthi Co. If the pain is intense they may be combined with morphine or belladonna, and if the gastric irritability is great, with hydrocyanic acid dilute.

As an *intestinal sedative* and *astringent* they are largely employed in all forms of **diarrhœa**, acute or chronic, either in children or adults. The salicylate is a useful remedy for children's diarrhœa due to the decomposition of food, because it has the properties of both bismuth and salicylic acid. Occasionally it may with advantage be combined with grey powder. It has also been found very useful in summer and tubercular, enteric and lienteric diarrhœa, or cholera. Bismuth salts are most effective remedies in **mucus diarrhœa** and **dysentery**. In the last disease they may be given with Dover's powder to check the after diarrhœa.

Syphilis.—Sauton and Robert have shown that tartrobismuthate of sodium and potassium is preventive and curative of fowl **spirillosis** as well as **trypanosomiasis**. Subsequently it has been found by French physicians to be of value in human **syphilis**. The advocates of this remedy maintain, that in doses which can be given intramuscularly safely, bismuth preparations have greater and more rapid therapeutic effect than mercury, that they may not be so quickly acting as arsenical preparations, but the effects are more permanent than those of arsenic. Small amounts are absorbed and enter the tissues where they possibly act as poison to the spirochætes, or at best inhibit their multiplication. Since it is not possible to introduce this drug in sufficient concentration to produce immediate result, the treatment is continued for a prolonged period in maximum tolerated concentration. There is no doubt that the organic aresenic compounds are more rapid in their effects and should get the preference in the primary stage of the disease. But all authorities agree that this requires to be supplemented by either mercury or bismuth. Some consider it superior to mercury in the treatment of congenital syphilis. They are of special value in those manifestations of the disease which are resistant to both mercury and arsenic. Since bismuth has been found in the cerebro-spinal fluid of treated cases and being neurotropic, favourable results are expected in the syphilis of the central nervous system. The results in general paralysis are disappointing, though it sometimes does good in tabetic crisis.

Lees summarises the value of bismuth in the treatment of syphilis as follows :—(1) It is more rapid in its effects than mercury but not so as the salvarsan group of drugs ; (2) the surface lesions are influenced as rapidly as arseno-

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benzol, but more rapidly than mercury; (3) combined treatment with bismuth and arsenic is more potent than either given separately, and if the therapeutic doses are not exceeded the treatment has no untoward effect; (4) metallic bismuth in isotonic glucose solution is free from pain and other side effects, and is better tolerated in this form than either arsenic or mercury; (5) this treatment is of special value in cases intolerant to arsenic or mercury; (6) it is best used as an adjunct to other treatment and should not be used alone, even in very earliest cases, except in cases showing intolerance to arsenic or mercury.*

Other uses.—In association with the Rontgen rays, bismuth has been largely used for diagnostic purposes in connection with diseases of the *gastro-intestinal tract*, but its place has now been taken by barium sulphate (*see* page 102), which is less expensive and just as effective.

Prescribing hints.—As the less soluble preparations allay irritation better than the soluble ones, they are to be preferred when gastric or intestinal irritability is a prominent symptom. If they are given in a mixture they should be suspended by the compound tragacanth powder, and not by the mucilage of acacia, as the latter may convert the mixture into a jelly-like mass. Again the subnitrate should not be combined with any alkaline carbonates, for bismuth oxynitrate slowly parts with nitric acid in water and gives off carbonic acid. Neither should they be mixed with iodides in a mixture as they turn yellow from free iodine and from formation of iodide of bismuth. These salts should not be used with preparations containing tannin which form insoluble tannate of bismuth.

In the treatment of syphilis bismuth preparations should be used intramuscularly, the intravenous injection of the soluble salts is so toxic that it is not used. The object is to form depots of slowly soluble compounds which may then be gradually and continuously absorbed. It has however the disadvantage of forming local fibrosis, when absorption of the drug from these depots becomes progressively impaired and finally arrested. Some patients show several of these nodules. This objection is less when potassium bismuth tartrate is used, as this is usually absorbed, or disappears from the site of injection in 2 to 4 weeks. Although soluble preparations are more quickly absorbed they are liable to produce severe local reactions and toxic effects. The B.P. preparations are quite as good as any of the numerous compounds placed on the market. Injectio Bismuthi is a suspension of finely divided metallic bismuth in glucose solution, and Injectio Bismuthi Salicylatis is a suspension in oil. It is customary to give small doses of

* British Medical Journal, Aug. 1927

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weekly injections, and 0.1 grm. of the tartrobismuth of potassium or the salicylate are given in 10 p.c. suspension in olive oil. After ten to fifteen injections it is necessary to wait till it is absorbed before starting with the second course. A point midway between the ischial tuberosity and the posterior superior iliac spine is chosen and sterilised by iodine. The needle is then thrust perpendicularly into the muscle. See that no blood comes out of the needle before giving the injection.

ARSENI TRIOXIDUM

Arsenic Trioxide

Syn.—Arsenic ; White Arsenic ; Acidum Arseniosum.
Syn. I.V.—*Sankia*, Hind. *Sanko*, Beng.
Source.—Obtained by roasting certain arsenical ores. Contains not less than 99. 8 p.c. As_2O_3.
Characters.—A heavy, white powder or irregular lumps having a vitreous fracture, containing frequently both transparent and opaque varieties. *Soluble* slowly in 65 parts of water, freely in acidulated water, or solutions of alkali hydroxides or carbonates ; slightly in alcohol (90 p.c.).
Incompatibles.—Lime water, iron salts, magnesia and astringents.
B.P. Dose.—$\frac{1}{60}$ to $\frac{1}{12}$ **gr. or 0.001 to 0.005 grm.**

Official Preparation

1. **Liquor Arsenicalis.** *Syn.*—*Fowler's Solution.*—Contains 1 p.c. w/v of arsenic trioxide, or about $\frac{1}{12}$ gr. in 8 ms. **B.P. Dose.—2 to 8 ms. or 0.12 to 0.5 mil.**

ARSENI TRIIODIDUM

Arsenic Triiodide

Syn.—Arsenii Iodidum.
Source.—Obtained by combination of arsenic and iodine, and purifying the product by crystallisation.
Characters.—Small, orange crystals. *Soluble* in 18 parts of water. 42 parts of alcohol (90 p.c.), in ether, chloroform and in carbondisulphide.
B.P. Dose.—$\frac{1}{16}$ to $\frac{1}{4}$ **gr. or 0.004 to 0.016 grm**

Official Preparation

1. **Liquor Arseni et Hydrargyri Iodidi.** *Syn.*—*Donovan's Solution.*—1 p.c. solution. Contains $\frac{1}{7}$ gr. of each salt in 15 ms. **B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**

Non-official Preparations

1. **Ferri Arsenas.**—A tasteless, amorphous greenish powder. *Dose.*—1/16 to 1/4 gr. or 0.004 to 0.016 grm.
2. **Sodii Arsenas Anhydrosus.**—A soluble white powder. *Dose.*—1/40 to 1/10 gr. or 0.0015 to 0.006 G.

Pharmacology

Externally.—Arsenic is a local **irritant** acting slowly on the tissues producing inflammation which may even cause

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sloughing. This irritant action is more marked on the denuded surface or mucous membrane. After prolonged application the cells die, but it is more destructive to pathological tissue than healthy cells.

Internally.—In small therapeutic doses it increases the gastric vascularity and secretion, and thus improves appetite and digestion. In large doses it is a powerful **gastro-intestinal irritant**, and causes severe inflammation of the whole digestive tract. The gastric mucous membrane becomes congested and swollen and even shows signs of hæmorrhage. It was formerly held that these symptoms were due to local action on the alimentary canal similar to that produced by strong acids or the caustic metals. They are, however, due to paralysis of the capillaries of the splanchnic area. As a result of this action there is exudation, œdema and increased peristalsis with watery stools which contain shreds of mucus and coagulated exudation forming the so-called rice water. Arsenic even when subcutaneously injected is excreted into the stomach. This view will not explain the fatty infiltration and cloudy swelling which are the specific effects of arsenic.

Blood.—The action of arsenic on the blood is not well understood, although it is used in some forms of anæmia. In normal person it diminishes the number of red cells though the hæmoglobin is unaffected, in fact it does not stimulate the production of red cells. The improvement may be due, as Stockman has suggested, to some specific effect on some undiscovered toxin or parasite, or as pointed out by Gunn to anti-hæmolytic action which protects the red corpuscles from destruction. Arsenic increases the leucoblastic elements of the bone marrow which becomes more vascular, and this may have some share in improving anæmia. Some hold that arsenic sets free some of the blood forming principles by causing destruction of a portion of the patient's liver.

Heart and circulation.—In isolated heart the amplitude is first increased and then diminished. Comparatively small doses directly paralyse the frog's heart making it slow, weak and irregular, which eventually stops in diastole. The mammalian heart is little affected, but in poisoning the muscles are directly depressed. The capillaries dilate enormously and the blood-pressure falls. This effect is due to the direct action of the drug on the capillary walls, specially those of the splanchnic area. Since the pressure falls even when the intestines are tied, it follows that besides the splanchnics other vessels are also dilated, the splanchnic vessels, however, are more susceptible to the action of arsenic than those of the rest of the body. The arsenites are more toxic than the arsenates and the inorganic preparations more than the organic ones.

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Metabolism.—In minute doses administered for a long time arsenic enjoys the reputation of increasing growth and nutrition by checking oxidation. The condition of the skin improves, the bones become longer and more compact and there is increased vascularity of the bone marrow. It is not clearly understood how these changes are brought about since the results of different observers have been different. While improvement in nutrition has been reported by some observers others like Stockman and Greig observed no change in the growth of animals under prolonged use. Small doses are supposed to increase the assimilatory processes and help storage of proteins. Large doses produce effects similar to phosphorus but of a milder nature. Prolonged use lessens the activity of the liver and reduces the formation of glycogen, which may disappear entirely. The liver becomes enlarged and the pressure in the bile duct prevents escape of bile into the duodenum, producing jaundice and allowing bile pigments to appear in the urine. There is increased protein breakdown and although the total nitrogen of the urine is not much altered, there is increased amount of urea, ammonia, leucin, tyrosin, etc. Fatty degeneration of the liver, kidneys, heart and muscles generally is evident. Binz and Schulz explain the action by supposing that it acts as a carrier of oxygen, which it receives and gives up, by transformation of arsenious to arsenic acid in the tissues and by the reduction of the arsenic into arsenious acid. This theory however does not explain all the effects of arsenic.

Nervous system.—Ordinarily no special action on the nervous system is elicited by arsenic. In acute poisoning no evidence of its action on the nervous system is observed as death takes place from gastro-intestinal irritation before any nervous symptoms can develop. Sometimes paralysis of the extremities appear with disturbances of sensation from central action, although they may be partially explained by the disturbances of nutrition. In chronic poisoning symptoms of peripheral neuritis develop with limited areas of paralysis.

Respiration.—We do not know much about its action on respiration except that habitual eaters of arsenic, such as the Styrian peasant, can undergo great exertion without much difficulty and distress of breathing.

Skin.—Arsenic has a marked effect on the nutrition of the skin, it improves the complexion and cutaneous nutrition, and increases the subcutaneous fat. It is eliminated with the sweat, and causes itching and eruptions, which may be erythematous, papular, pustular, furuncular, pigmentary or urticarial. These effects may be due either to some specific action produced by the drug upon the epithelium of the skin during excretion, or increase of lymph

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to the part. The most characteristic action is the darkening of the skin, "*arsenical melanosis*," which may vary from slight pigmentation to a deep brownish-red, and is due to deposition of some organic compound in the deeper layers of the corium.

Toleration.—Long continued use leads to tolerance, so that quantities which would otherwise cause toxic symptoms are taken without any ill effects. The peasants of Styria take arsenic to improve their complexion and power for work and they can undergo extreme bodily exertion without any respiratory distress. It is not known how this tolerance is established, although it is possible that long continued use may help formation of some antitoxin, or that the body is able to fix it in some non-toxic form. Some hold that absorption is so delayed that acute poisoning does not occur and in support of this view mention that arsenic eaters suffer from the symptoms of poisoning when the drug is administered in solution or hypodermically. It is evident that there is no true tolerance and that the body cells remain susceptible to arsenic. Housman attributes it to increased excretion. He has further shown that corrosive action of arsenic on the gut is diminished by habituation.

Elimination.—It is excreted chiefly in the urine and to some extent in the fæces. A small percentage is also excreted in the bile, sweat, saliva, tears and milk. The excretion begins within two to eight hours after administration. Given by the mouth it is excreted by the intestine, while used hypodermically it is eliminated largely by the kidneys. Its elimination is very slow, and traces may be recovered two or three weeks after stoppage of its use. Less than 20 p.c. appears in the urine and fæces in the first 24 hours. The arsenic retained is distributed throughout the body, a considerable amount being stored in the liver and is slowly got rid of in the hair and epidermis where it may be found for months even after the drug has disappeared from the urine and fæces.

Acute toxic action.—Colicky pains, severe vomiting and purging, cramps of the legs, intense thirst, prostration and collapse are the prominent symptoms, which may be mistaken for those of cholera. At the *post-mortem* the stomach and intestine are found inflamed, with occasional patches of softening of the mucous membrane. *Fatty degeneration of the liver, kidneys, and heart* is found if the patient survives long enough. In fulminant cases there may be no symptom of gastro-enteritis, death takes place from collapse due to withdrawal of blood to the splanchnic area before enteritis develops.

The fatal dose varies, 0.1 to 0 3 gm. of trioxide is usually fatal.

Antidotes.—Emetics, apomorphine. The pump must be used with great caution. Moist peroxide of iron freshly prepared by mixing solution of ferric chloride with sodium or ammonium carbonate and straining rapidly through muslin, or dialysed iron in 1 oz. doses diluted, or better still ferri hydroxidum c. magnesii oxido. Demulcents, and castor oil to clear the intestine, stimulants, hot-water bottles etc.

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Chronic toxic action.—Chronic poisoning occurs amongst those who either handle arsenical pigments, inhale arsenical dust from wall-paper, dresses, etc., or consume wines* containing traces of arsenic. Loss of appetite, nausea, vomiting, colic, mild diarrhœa, œdema of the lower eyelids, conjunctivitis, swelling of the joints are the symptoms generally observed, when arsenic is continued long medicinally in large doses. Peripheral neuritis, muscular paralysis of the limbs, ataxic gait, muscular atrophy, bronzing and patchy pigmentation of the skin and darting pains in the limbs are also noticed in many cases of slow poisoning. Skin eruptions are a common accompaniment and are due to the direct action of the drug. Irritation of the mucous membranes of the eye, nose and larynx follows and is analogous to skin eruption.

THERAPEUTICS

Externally.—Arsenic was formerly extensively used as a caustic in the form of paste for destroying new growths, such as lupus, condyloma, epithelioma, warts, etc. Its use has been superseded by surgical measures, radium and deep X-ray. Arsenical cigarettes are sometimes smoked for the relief of asthmatic fits, but such inhalation must be given with caution.

Internally. **Gastro-intestinal tract.**—Dental arsenical paste is employed to destroy the tooth-pulp in caries of the tooth, before stopping. In minute doses *before* meals, arsenic may be given in irritative dyspepsia, vomiting of habitual drunkards, vomiting or diarrhœa excited by food and gastric neuralgia. For other diseases of the alimentary tract, it is given *after* food.

Lungs.—Arsenic has been used in the treatment of asthma and its prolonged administration checks asthmatic fits. It has also been used in the treatment of phthisis where it appears to act as a general tonic and has no specific action on the tubercular lesion.

Malaria.—Arsenic is used in the treatment of malaria, and its value is more marked in chronic cases accompanied by anæmia and cachexia. Its effect in acute cases is not so marked as quinine, but given with iron and quinine after the acute stage, it is certainly of great value. In cases where quinine fails to effect a cure, a combination of quinine and arsenic will be found to yield better results. The following prescription will be found very useful in chronic cases with anæmia and cachexia. Arseni trioxidum gr. $\frac{1}{24}$, quinine sulphate gr. 2, ferri sulphas gr. $\frac{1}{4}$, ext. nucis vom. sic. gr. $\frac{1}{4}$, salicin gr. 1, pil. rhei co. gr. $1\frac{1}{2}$. Twice a day after food. The writer considers arsenic to be a useful remedy for arresting the paroxysmal febrile attacks of elephantiasis arabum, but it must be continued for a long time.

Nervous system.—In large doses arsenic is an old remedy for chorea, but with our advancing knowledge of the

*Peripheral neuritis was a marked symptom in an outbreak of arsenical poisoning in England, due to drinking contaminated beer.

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ætiology of this disease, its place has partly been taken by the salicylates. The disadvantages of giving arsenic in large doses are: (1) it sets up gastro-intestinal irritation; (2) it may cause severe neuritis. Children over 4 or 5 years of age can bear as large doses as adults.

Lymphomas.—In Hodgkin's disease (general lymphadenoma), no remedy is known to be of any use except arsenic. Large lymphomas are said to have been absorbed by the continued use of arsenic internally and hypodermically into the tumours.

Anæmia.—Arsenic is used in pernicious anæmia where it improves the number of red blood corpuscles and the hæmoglobin, in leukæmia it is often used in large doses, but the beneficial effects of arsenic in these conditions appear to be only of a temporary nature. Arsenic is also useful in *microcytic anæmia* and in anæmia following malaria, specially when combined with iron. Some clinicians use it in chlorosis, but it appears that beyond the general improvement of nutrition and lessening breathlessness and to a certain extent acting as a heart tonic, it has no specific action in chlorosis when used alone.

Skin.—Chronic skin diseases, especially scaly and papular varieties, are wonderfully benefited by arsenic. Psoriasis, lichen, chronic eczema, acne, pemphigus, etc., yield to it. It seems to act specially well in diseases affecting the epidermis rather than other portions of the skin.

Caution.—(1) Do not use arsenic during the inflammatory stage of any cutaneous disease.

(2) Always administer after food and well diluted, except where its local action on the stomach is desired.

(3) As soon as itching, smarting, or irritation of the conjunctivæ, œdema of the lower eyelids, pain on the pit of the stomach, or symptoms of neuritis are noticed, the dose must be reduced to one-fourth or one-fifth. If the irritation does not subside it must be further diminished, or stopped altogether.

(4) If the skin becomes irritated, a laxative may be given, rather than the treatment be stopped.

(5) For the radical cure of chronic skin disease it must be continued for some months after the final disappearance of eruptions.

(6) Children over 5 years of age can bear as large doses as adults. Old people bear it badly.

Prescribing hints.—Solid arsenic is given in pill. Sometimes it is used hypodermically, as in multiple sarcomas, but with doubtful benefit. For prolonged use Fowler's solution is the best preparation, and the dose should be slowly increased to its therapeutical limit of tolerance. It is contra-indicated when gastric or intestinal irritation is present, such as nausea, loss of appetite, etc.

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Organic Arsenic Preparations

Within recent years these compounds have come to occupy an important position among the therapeutical agents for the treatment of several protozoal diseases, notably syphilis and trypanosomiasis. They belong to two groups, *viz. trivalent* and *pentavalent* forms, in both of which the arsenic exists in non-ionisable form and therefore they can be given in large doses. They are less toxic than the inorganic salts, and do not possess the specific paralysing effect on the capillaries. They however do not produce their typical action immediately, but are slowly reduced in the body into ionic form by oxidation and other processes, when they become active. They are specially toxic to the invading parasite, though very little parasiticidal effect is seen *in vitro*, possibly they require the co-operation of the host to become parasitotropic.

1. Trivalent Compounds

NEOARSPHENAMINA

Neoarsphenamine

Syn.—Novarsenobenzol; Neosalvarsan; Novarsenobenzene.

Source.—May be prepared by treating 3:3′ diamino-4:4′ dihydroxyarsenobenzene with sodium formaldehydesulphoxylate. It is distributed in hermetically sealed glass phials, from which air has been excluded, or replaced by an inert gas. Contains about 20 p.c. arsenic.

Characters.—A yellow, dry powder, freely mobile in contact with glass surface; odour, none, except that due to traces of ether or alcohol. *Soluble* in water, insoluble in dehydrated alcohol. A 1 p.c. w/v aqueous solution is neutral, or slightly alkaline, to litmus.

B.P. Dose.—0.15 to 0.9 grm. or 2½ to 14 grs. (intravenous injection).

SULPHARSPHENAMINA

Sulpharsphenamine

Syn.—Sulpharsenobenzene. "Sulfarsenol."

Source.—Prepared by treating 3:3′-diamino-4:4′-dihydroxyarsenobenzene dihydrochloride with formaldehyde and sodium hydrogen sulphite. Supplied in sealed glass phials like neoarsphenamine. Contains about 20 p.c. arsenic.

Characters.—A yellow, dry powder, freely mobile in contact with glass surface; no odour, except of alcohol or ether. *Soluble* in water; insoluble in alcohol (95 p.c.), and in ether.

B. P. Dose.—0.1 to 0.6 grm. or 1½ to 10 grs. (subcutaneous or intramuscular injection).

ARSPHENAMINA, U. S. P.

Dioxy-diamino-arseno-benzol Di-hydrochloride

$C_{12}H_{12}O_2N_2As_2(HCl)_2\ 2H_2O$. (Not official)

Syn.—Arsenobenzol; Salvarsan; 606.

Source and characters.—A light yellow powder, odourless or has a slight odour. Hygroscopic. In the dry state or in solution it is

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oxidised by exposure to the air, becoming darker and more toxic. Soluble in water, alcohol, and glycerin. Contains not less than 30 p.c. of arsenic.

N.B.—Preserve in sealed colourless glass tubes from which air has been excluded either by production of a vacuum or by displacement with a non-oxidisable gas.

Dose, U.S.P.—Intravenous, 0.4 grm or 6½ gr.

Preparation of solution.—*Intramuscular.*—Place the required salvarsan in a small procelain dish and rub it with 9 to 10 drops of sodium hydroxide solution 15 p.c. by weight, then add (carefully rubbing all the time with a glass rod) drop by drop required amount of *fresh distilled water*, about 5 to 10 c.c. Neutralise the solution by the addition of sodium hydroxide or dilute hydrochloric acid.

Intravenous.—Place 30 to 40 c.c. physiological salt solution in a 300 c.c. stoppered bottle, add to this 0.6 grm. of salvarsan. Dissolve it by thorough shaking, add 23 drops of 15 p.c. sodium hydroxide solution. A precipitate forms which quickly re-dissolves. Dilute the remaining clear yellow solution to 300 c.c. with normal saline solution.

Each 50 c.c. is equal to 0.1 grm. Therefore 150 c.c. form the average dose for women and 200 c.c. for men.

Non-official Preparation

1. **Silver Arsphenamine.** *Syn.—Silver Salvarsan.*—First introduced by Danysz under the name of **Luargol.** An improvement of this preparation is **Neosilver Salvarsan,** which contains 20 p.c. of arsenic and 15 p.c. of silver. It is a chemotherapeutically activated neosalvarsan and considerably detoxicated by the introduction of silver.

Dose.—0.1 grm. to 0·6 grm. in 10 c.c. of water intravenously, at an interval of not less than 4 days for men. 0.1 grm. equals 0.3 grm. of neosalvarsan.

2. Pentavalent Compounds

1. **Acidum Cacodylicum.**—It is dimethyl-arsonic acid, soluble 2 in 1 of water and 1 in 4 of alcohol (90 p.c.). Its effects are more or less like inorganic salt to which it is partly reduced in the body. Changes take place slowly and the action is prolonged. It imparts an odour of garlic in the urine, sweat and breath. *Dose.*—¼ to 1 gr. or 0.016 to 0.06 G. The chief cacodylate preparations are:—

2. **Ferri Cacodylas.**—A yellowish, amorphous powder; soluble 1 in 15 of water. *Dose.*—¼ to ½ gr. (0.016 to 0.03 G.) in pills three times daily. ¾ gr. (0.05 G.) *hypodermically* daily. Chiefly used in *anæmia* and *chlorosis.*

3. **Guaiacol Cacodylas.** *Syn.—Cacodyliacol.*—Chiefly used in *tuberculosis. Dose.*—½ to 2 grs. or 0.03 to 0.12 grm. *per os:* or dissolved in sterile oil *hypodermically.*

4. **Strychninæ Cacodylas.**—A white crystalline powder slightly soluble in water. Chiefly used in those conditions in which a combination of strychnine and arsenic is required. *Dose.*—1/30 to 1/10 gr. or 0·002 to 0·006 G.

5. **Sodii Cacodylas, U.S.P.**—*Sodium Dimethylarsonate.*—In white, colourless, deliquescent prisms, or as granular powder. It is used in all cases in which arsenic has been used, and is valuable in chronic skin affections and *phthisis.* Given in doses of 1 to 2 grs. *intramuscularly.* Therefore it can be used with less danger of upsetting the stomach. It may also be given in pill form. *Dose.*—*Hypodermically,* ½ to 1 gr. (0·03 to 0·06 G.), but it may be increased to 3 grs. as *maximum single dose;* and as *maximum dose* in 24 hours. If given by mouth or per rectum it may cause renal congestion with a fall of urinary secretion. *Dose, U.S.P.*—0.06 gm. or 1 gr.

6. **Di-sodium Methylarsonate.** *Syn—Arrhenal, "New Cacodyle."*—Soluble 1 in 1 of water and sparingly in alcohol. Its arsenic content is 27.35 p.c. Its uses are the same as sodium cacodylate.

Dose.—½ to 2 grs. or 0·03 to 0·12 G. by mouth, or hypodermically; the *maximum dose* (single or in 24 hours) being 3 grs.

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7. **Sodii para-aminophenylarsonas.** *Syn.—Soamin, Atoxyl, Arsamin.*—A white crystalline powder with a saline taste, soluble 1 in 3 of water at body temperature. Solutions, which should be freshly prepared, may be sterilised by boiling five minutes without becoming decomposed. Its arsenic content should be at least 22.8 p.c.

Dose.—Per mouth, 3/4 to 3 gr. or 0.05 to 0.2 grm. twice daily after food. *Maximum daily dose.*—3 grs. *Hypodermically*, 1 to 3 grs. or 0·06 to 0·2 G. *intramuscularly* high up into upper third of buttock on alternate days. The salt should be dissolved in sterile water. *The maximum of 3 grs. cannot be exceeded with safety.*

Uses

Atoxyl has been used in **syphilis** intramuscularly, and provided the precautions to be hereafter noted are attended to, no bad effects or signs of toxicity should follow.

In **trypanosomiasis**—human and animal—soamin has been largely used with some success, but in many cases recurrence of the disease has occurred.

Soamin and the cacodylates have been used with success in anæmia, locomotor ataxy, relapsing fever, pellagra, cerebro-spinal meningitis, tuberculosis and chronic skin diseases (psoriasis and lichen).

Hypodermically it has been found to be of great value in **bronchial asthma** with eosinophilia (Ghosh, *Glasgow Medical Journal*, 1919) in 1 gr. doses, increased to 3 grs. given twice a week. Administration of alkalies helps in its action.

Precautions.—Several cases are on record of blindness due to optic atrophy following its use. This possibly was due to an unsafe dosage being used, but as idiosyncrasy and previous optic degeneration are important factors, it is necessary to proceed with caution when using the remedy. The following are points to which attention should be paid:—

1. Always examine the retina and the disc for degenerative changes before commencing a course of treatment, and if normal, periodically test the vision and look for any contraction of the fields—if any contraction is noticed stop use of the remedy.

2 In cases of renal and hepatic disease, and in arteriosclerosis, do not use the drug, and only use it with great caution for this reason in old patients.

3. When 100 grs. have been given stop for four weeks.

The earliest toxic symptoms to be carefully watched for are insomnia, gastric pain and haziness of vision.

8. **Arsacetin.** *Syn.—Sodium Acetyl-p-aminophenylarsonate.*—It has been used in *syphilis* and *trypanosomiasis.* It is also useful in *anæmias*; in such cases however a smaller dose, *viz.* 0.1 grm. to 0.5 grm., should be given subcutaneously. As with atoxyl caution in its use is to be recommended, as cases of blindness have been reported after its use.

Dose—3/4 to 3 grs. per os, three to four times daily. *Intramuscularly* a maximum of 3 grs. in 10 p.c. solution should not be exceeded.

9. **Tryparsonum.** *Syn.—Tryparsamide.—Sodium-N-phenyl-glycinamide-p-arsonate.* A pentavalent arsenic compound in white powder, soluble in water. Usually given in 20 p.c. solution. Contains 25.32 p.c. arsenic. Quickly absorbed when given subcutaneously, may be used *intramuscularly* or *intravenously. Dose.*—0·5 to 3 grm. in 10 c.c. of water *intravenously*, once a week in *trypanosomiasis.*

10. **Acetarsol, B.P.C.** *Syn.—Stovarsol.—Acetyl-amino-hydroxyphenyl-arsonic acid.* A pentavalent compound introduced for the treatment of amœbic dysentery. Contains about 27 p.c. of arsenic. *Dose.*—By mouth, 4 gr. or 0.25 gm. for adults, 2 or 3 times a day, for seven days. **Bismuth-stovarsol** or **Bistovol.** *Dose.*—2 grm. *per os* daily; ampoules of 3 c.c. in 10 p.c. oily suspension for injection.

11. **Acetylarsan.**—*Oxy-acetylamino-phenyl-arsonate of diethylamine.* Contains 23.6 p.c. of arsenic. A simple derivative of stovarsol in white crystalline substance soluble in water. Can be given subcutaneously without any local effects.

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Used in *hepatitis* and *amœbiasis* with emetine. Also destroys cysts. Eliminated in 36 hours. In lambliasis. *Dose.*—1 to 2 c.c. *intramuscularly*, followed by 8 to 10 weekly injections of 5 c.c.

Pharmacology of Arsenobenzol Derivatives

Arsenical preparations have been largely employed from early times in the treatment of syphilis, and the great endeavour in modern days had been to find a preparation which would have a *parasitotropic* effect, but will not have any *organotropic* property. These drugs possess a maximum parasitotropic with a minimum organotropic property.

The introduction of salvarsan as a remedy for syphilis is the direct result of the chemotherapeutic studies of Ehrlich, who suggested a parasiticidal action of the drug. Certain side chains of the drug possess a selective affinity for certain side chains of the protoplasm of the spirochæte, and the drug kills the germs at a concentration harmless to the tissues of the host. This theory however is open to doubt. These organic compounds undergo certain changes in the body tissues when they exert an action either on the parasites or on the host. The arsenic in arsenobenzol exists in trivalent form; and Voegtlin has suggested that it is inactive in this form but becomes active when it is partly oxidised in the tissues. It circulates in the blood in the colloidal form and is very soon deposited in the tissues. It is believed that salvarsan is deposited in different organs in relatively non-toxic form and that it is doled out in more active form, which acts more powerfully on the *spirochætes*.

The mode of action of these compounds appears to be an indirect one, and the presence of arsenic within the reticulo-endothelial cells has actually been demonstrated,* while splenectomy experiments in spirochætal infections have established that infections held in check in animals break into acute manifestations in splenectomised animals and that treatment of these with specific drugs is less effective than in non-splenectomised animals. In fact there is evidence to show that the mortality rate is increased and the cure rate is decreased after splenectomy, and that an intact reticulo-endothelial system is necessary for the full functioning of the chemotherapeutic compounds of arsenic. The different ways the reticulo-endothelial system acts has already been discussed (*see* page 423).

Given intravenously in increasing doses, salvarsan causes dilatation of the heart, rise of pulmonary pressure and a slow fall of systemic pressure. The heart is depressed depending on the concentration and reaction of the solution used, acid solutions being specially toxic.

Absorption and elimination.—Absorption is very slow

* Jiminez de Asua and Kuhn, 1928

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even when given intravenously. Very little is absorbed by the rectum. With neoarsphenamine the kidneys contain the most arsenic, then the spleen, the liver, thyroid, adrenals, heart, muscles, etc. Although after long continued use large quantities may be stored in the different organs of the body, it is doubtful whether this arsenic is therapeutically active, or capable of being rendered so after reabsorption into the blood. Wechselmann, Lockemann and Ulrich have shown that the stored arsenic is therapeutically inactive, it is only during the short period when the arsenic is in the blood that its maximum effect is exerted.

It is broken down in the body and excreted in the urine and fæces as ionised arsenic. The percentage of arsenic after salvarsan given intravenously is greater in the fæces than in the urine, although it appears in the urine within a few hours, and not till the third or fourth day that it is found in the stool. The greater part found in the stool is due to rapid elimination through the bile which has a high arsenic content. Excretion is slow after intramuscular injection, and the maximum quantity eliminated in 24 hours after an intravenous injection of salvarsan is about 10 mg., *i.e.*, about 3 p.c. of arsenic contained in 0.9 gm. The excretion is said to be hastened by the administration of potassium iodide. The pentavalent compounds are excreted more rapidly, about 85 p.c. being eliminated within 24 hours. Igersheimer and Rothmann have found that after injection of atoxyl 90 p.c. was excreted unchanged in the urine, 3 p.c. was reduced to trivalent form, 2 p.c. was excreted with the stool, and 2.3 p.c. was retained in the body. The rate of excretion shows wide individual variation which accounts for the difference in toxicity and therapeutic activity. Damage to the kidneys causes considerable variation in the rate of excretion.

After an intravenous injection the drug must circulate through the brain and the cord, but whether it penetrates the cerebro-spinal fluid has received much attention. While some observers found no trace of arsenic in the brain after intravenous injections of arsphenamine, others (Fordyce, Rosen and Myers) detected in more than 80 p.c. of cases, at least during the period of treatment.

Toxic symptoms and other side effects :—

As a rule few cases show any symptoms of poisoning when arsphenamine is injected. According to individual variation, cases have been observed where symptoms of poisoning appeared, and these effects varied from simple disturbance to grave and even fatal issues. Some of these cases were no doubt due to faulty technique, others from some form of aresnical poisoning, while a few were due to alteration in the colloidal equilibrium of the blood following an injection of a large bulk of fluid. The symptoms may be grouped as follows :—

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1. *Immediate reactions.*—In about half to five per cent. of cases severe toxic symptoms appear within a few minutes. Although alarming they are rarely fatal. The face becomes flushed, the conjunctiva injected, tongue and eyelids become œdematous. Nausea, vomiting, profuse perspiration, cough, dyspnœa and precordial pain are often present. If stomatitis is present there may be pain in the gums and teeth, or in more severe forms the tongue and lips may become swollen. These symptoms are known as *nitritoid reaction*. The exact cause of this immediate reaction is still a matter of speculation. They are common with patients with tubercular lesions (Stokes), or when a large volume of fluid is injected, as with salvarsan. They are probably due to some alteration in some blood proteins (flocculation and agglutination), or to the presence in the blood of the break-down products of spirochætes, or to liberation of a histamine like substance.

Occasionally the syphilitic process may show an increase in an acute form after the injection. There may be an exacerbation of a syphilitic keratitis resulting in blindness, or deafness, or development of other types of acute lesion of the central nervous system. If the secondary skin lesions are present they become erythematous, swell up and show an increase of secretion from the ulcers. This phenomenon, which is known as *Herxheimer reaction*, comes on suddenly and is due to the poisonous action of the proteins set free from the spirochætes. The appearance of any of these symptoms implies that the treatment should be stopped.

2. *Early toxic symptoms.*—These generally appear within a few hours after administration and are characterised by febrile reaction with chill, nausea and vomiting. There may be severe pains in the body. Kidneys show evidences of damage with albumin and casts. As a rule these may be temporary and the symptoms disappear with the stoppage of treatment. Urticarial and other forms of skin eruptions may appear *(exfoliative dermatitis)*. These generally appear after about a week and may be very severe. Although sulpharsphenamine is supposed not to cause skin eruption, the writer had a severe case of exfoliative dermatitis following the use of this preparation.

3. *Severe late reactions.*—Occasionally severe and even fatal symptoms appear a few days after administration. In addition to some of the symptoms already described, the cerebrum and the liver are involved.

The cerebral symptoms (*arsphenamine encephalitis*) appear after large doses, or when the ordinary doses have been given too quickly. The onset is sudden, the symptoms being headache, vomiting, dyspnœa, epileptiform convulsion with clonic spasms, followed by unconsciousness, suppression of urine, dilated pupil, coma and death, generally forty-eight hours after the onset of the symptoms. Hæmorrhagic

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encephalitis occurs during the secondary stage, as a rule after the second injection.

Jaundice appears in the course of treatment and may start suddenly, may be intense and may end fatally. Three types of jaundice are usually found ; they are :—

(*a*) *Early jaundice*, usually commences within a few hours, may appear suddenly, or after subsequent injections.

(*b*) *Late jaundice* is a more serious disorder and appears several weeks to several months after termination of a course of injections. Unless followed by acute yellow atrophy of the liver, recovery takes place. Liver may be enlarged, with bile and traces of albumin in the urine.

(*c*) *Acute yellow atrophy of the liver* is a more serious complication and appears some weeks after the end of a course of treatment.

The following factors influence toxicity :—(1) Abnormal toxicity of the drug ; (2) errors in technique ; and (3) susceptibility of the patient ; and are avoided by (1) using a reliable preparation ; (2) following the same technique in the preparation and administration of the drug ; (3) a preliminary examination of the patient for possible visceral disease ; and (4) watching the patient during the whole course of treatment.

Treatment of poisoning.—Since the symptoms of nitritoid reaction resemble anaphylaxis and nitrite poisoning, adrenaline and atropine are suitable remedies. By giving one-tenth of the dose an hour before the remainder is given, the toxic symptoms may be averted. The patient should be carefully watched for any of the late toxic symptoms during a course of treatment and if any appear, further treatment should be suspended. Nephritis and other symptoms are treated on general lines. Sodium thiosulphate is useful in arsenical dermatitis (*see* p. 84).

Therapeutics

These preparations are largely used in certain types of protozoal and spirochætal infections, and are of special value in syphilis, Vincent's angina, yaws, etc., and good results have been reported in relapsing fever and rat-bite fever. A single injection of arsenobenzol or any of the derivatives will cause the spirochætes to disappear in a few hours from the chancre, and since a single dose will not reach all the parasites, the injections are repeated. After three injections the Wassermann reaction if positive becomes negative in most cases, but the improvement is not permanent, for after some weeks or months the reaction reappears and the symptoms of secondary syphilis begin to appear. It is therefore necessary that mercury should be given after these injections and continued on the usual lines. The

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advantage of using arsenobenzol is the rapidity of its action, whereas the concentration required to sterilise the system with mercury is obtained after several days or weeks. Therefore after the immediate action has been obtained by the use of arsenic the treatment should be supplemented by the slow and prolonged action of mercury.

The modern conception of the treatment of syphilis with arsenobenzol compounds is not to use a large dose to produce a high concentration of the drug in the blood for a limited period, but to maintain a moderate concentration for a prolonged period, by giving a series of injections in moderate doses instead of a single large dose. It has therefore been found necessary to give intramuscular injections more frequently so as to maintain a moderate concentration of arsenic for a prolonged period to effect complete recovery.

Some cases of syphilis do not improve under arsenobenzol and Ehrlich suggested that the failure was due to the parasites inhabiting in out of the way parts of the body, *e.g.*, cerebro-spinal fluid, which the drug could not reach. After an injection most of the parasites in the blood stream are killed, but a few surviving ones slowly multiply and reinfect the whole system.

In the treatment of syphilis arsenobenzol is the drug of choice in early cases (chancre and secondary manifestations) affecting young healthy persons. Novarsenobenzol is preferred for elderly people, pregnant women, children and patients with cardiac, renal and other complications. Silver salvarsan is useful in neurosyphilis, extensive gummatous ulcerations and anæmia. But since the preparation of the solution of salvarsan is complicated, and not suited for routine use, and was followed by a large number of accidents from errors in technique, neosalvarsan has practically replaced it and is extensively used.

Salvarsan and neosalvarsan have been used in malaria, yellow fever and human trypanosomiasis, but the results have not been encouraging. On the other hand *tryparsamide* is of special value in trypanosomiasis and effects a cure in early cases when given in 2 grm. doses intravenously every week for five injections. These are generally preceded by five injections of Bayer 205. The only disadvantage is that it causes limitation of the field of vision and sometimes even blindness. A few develop jaundice. It has little power in killing spirochætes and is not of any value in either primary or secondary stages, or against gumma, but it has the *power of penetrating the central nervous system* more readily than other arsenical preparations. It has not proved successful in the treatment of early manifestations of cerebro-spinal syphilis, but gives good results in disseminated sclerosis when given before irreparable damage of the nerve cells have resulted and may be combined with

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malaria treatment. It is said to possess remarkable power of reinforcing processes of natural resistance and promoting recuperation. It has also been used in filarial infection and chyluria with some success.

Stovarsol (acetarsol) is therapeutically active when given by the mouth, and is useful in amœbic dysentery specially of the encysted variety. Cases resistant to emetine often yield to it. It is also useful where emetine is contra-indicated. It has been used in yaws, syphilis, trypanosomiasis and filarial infections, but the results were disappointing.

Contra-indications.—(1) The injection should never be given on a full stomach, or when the blood-pressure is high. (2) It should not be given to persons suffering from chronic renal disease (of non-syphilitic origin), diabetes, or chronic myocardial degeneration, or to cases exhibiting evidences of recent endocarditis. (3) Owing to the congestive action of this drug it should not be used in cases with signs of active pulmonary tuberculosis, fetid bronchiectasis, or serious lung disease. (4) Patients whose vessels are atheromatous or who have suffered from cerebral hæmorrhage are also bad subjects for salvarsan. (5) Persons showing special idiosyncrasy to arsenic. (6) Persons suffering from non-syphilitic retinal diseases or affections of the optic nerve. (7) Advanced cerebral mischief and cachexia.

Method of administration.—Solution of arsenobenzol or novarsenobenzol given subcutaneously produce local irritation and inflammation. These effects are due partly to the drug and partly to the reaction of the solution, acid solutions cause severe and persistent pain, while alkaline solutions produce corrosion, ulceration and even gangrene. Neoarsphenamine though forms a neutral solution also produces severe pain, inflammation and fibrosis. Rectal administration has also been suggested but Mehrtens found that 4 grm. of neosalvarsan produced a concentration of 0.025 mg. arsenic per 100 c.c. of blood, while intravenous injection of 0.6 grm. produced at first 0.97 mg. per 100 c.c. and subsequently 0.077 mg. per 100 c.c. of blood. Rectal administration therefore is not so effective. The usual method is the intravenous route. It is practically painless, and there is seldom objectionable local effects at the point of injection ; if any should arise it may be ascribed to faulty technique. Moreover the time spent in bed is greatly reduced by this method. Whatever method is used strictest asepsis must be maintained. These injections should be followed by mercurial treatment, and usually injections of calomel or mercurial cream are given. When intensive treatment is required, a series of six intravenous injections, once a week, constitutes a course. But usually three injections are given at fortnightly intervals. The highest dose of salvarsan for a healthy adult man of average weight

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is 0.5 gm. intravenously, and 0.4 gm. for a woman. For a child ten pounds in weight the first dose should not exceed 0.01 gm. The maximum dose for a healthy adult Indian is somewhat lower, preferably 0.4 gm. of salvarsan for a man and 0.3 gm. for a woman. The dose of neoarsphenamine is greater than salvarsan in the proportion of 3 to 2, *i. e.* 0.6 gm. of neoarsphenamine equals 0.4 gm. of salvarsan. The dose should always be varied with the strength and condition of the patient. It has been found that smaller doses frequently repeated give as good results as full doses and are less dangerous to the patient.

Injection of Salvarsanised Serum.—Since very little arsenic passes into the central nervous system, intravenous use of salvarsan is not very useful in cerebro-spinal syphilis. It has therefore been suggested that in these cases salvarsanised serum may be injected directly into the spinal canal. The results have been rather hopeful specially in the treatment of tabes.

Swift-Ellis Method—The patient is given an ordinary dose of salvarsan or neo-salvarsan intravenously, and after an hour 40 c.c. of blood is withdrawn from a vein, which is allowed to clot and left for 24 hours on ice ; 12 to 15 c.c. of serum is then drawn off and centrifugalised. This serum contains about 0.01 mg. of salvarsan per c.c. It is heated to 56°C. for half an hour. This may be diluted with normal saline to make 30 c.c. and injected by lumbar puncture, an equal volume of cerebro-spinal fluid being first withdrawn. The injections are safe and may be repeated after two weeks.

POTASSII IODIDUM

Potassium Iodide. KI

Source.—Obtained by the action of excess of iodine on a solution of potassium hydroxide, evaporating to dryness, fusing with charcoal, and purifying by crystallisation from water. Contains not less than 99 p.c. of potassium iodide.

Characters.—Colourless, transparent or somewhat opaque, crystals, or a white granular powder. Odourless; taste, saline, slightly bitter *Soluble* in 0.7 parts of water, in 12 parts of alcohol (90 p.c.), in 2 parts of glycerin.

Incompatibles.—Bismuth subnitrate, spiritus ætheris nitrosi, solutions of ferric salts, dilute hydrochloric acid, liq. strychnine, potassium chlorate, alkaloidal salts, and substances containing starch.

B.P. Dose.—5 to 30 grs. or 0.3 to 2 grm.

SODII IODIDUM

Sodium Iodide. NaI

Source.—Prepared from iodine and a solution of sodium hydroxide by a process similar to that adopted in making potassium iodide: the salt being crystallised at a temperature not less than 20°C. Contains not less than 99 p.c. of pure sodium iodide

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Characters.—A white, crystalline powder, deliquescent, having a a saline and somewhat bitter taste. *Solubility.*—Less than 1 part of water, 1 in 3 of alcohol (90 p.c.).

B.P. Dose.—5 to 30 grs. or 0.3 to 2 grm.

Non-official Preparation

1. **Ammonii Iodidum.**—In minute colourless cubical crystals, or as white granular powder. Odourless, with a sharp saline taste. Very hygroscopic. Becomes yellow or brownish when exposed to air and light.

Dose.—2 to 6 grs. or 0·12 to 0·4 grm.

Pharmacology of Iodides

Internally.—The action of iodides is identical with that of iodine, except that these are less irritant to the gastro-intestinal tract, and are therefore used in preference to iodine. Large doses cause irritation of the stomach and give rise to nausea and vomiting if used in concentrated solution.

Iodides are absorbed by the intestine and circulate in the blood as iodide through which it penetrates the different tissues of the body. The acid in the stomach may liberate highly irritating iodine. They are excreted with the saliva within a short time and give a metallic taste in the mouth. In large doses they produce a group of symptoms known as **iodism.** Besides the characteristic action of iodine they increase the secretion of bronchial glands during elimination through the respiratory mucous membrane, producing a flow of thin mucus, and liquefying tenacious secretion. Potassium iodide tends to lessen viscosity of the blood, dilate peripheral arterioles and reduce irritability of the heart without affecting its contractility.

They are **diuretics,** and are more powerful than chlorides. They act possibly by diminishing reabsorption from the tubules.

Excretion of lead and mercury fixed by the body is made rapid by potassium iodide. It forms insoluble, unabsorbable and non-poisonous lead iodide.

As the spirochætes of syphilis are not killed by the application of iodide to a syphilitic lesion, it does not act as a parasiticide. The specific effects in the tertiary stage are exerted not on the parasites but upon the tissues in which the parasites live and which have reacted to their presence by the formation of gumma. These dissolve under the action of iodides. They combine with antitrypsin which normally prevent the resolution of necrotic tissue and set free proteolytic ferments which digest and absorb gummatous tissue.

Iodine is contained in the form of thyroxine in the thyroid gland, and administration of iodine or iodides increases the iodine content of the gland with corresponding increase of its activity.

Elimination.—Iodides are rapidly eliminated mainly by

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the urine, but partly also by the saliva, gastric juice, sweat, milk, and other secretions and body fluids and effusions. Seventy-five per cent. of the dose appears in the urine within twentyfour hours. The remainder may remain in organic combination in the body. Swift reported that iodine was not found in the cerebro-spinal fluid even after very large doses given by the mouth. Later Campbell and Snodgrass demonstrated iodine in the same fluid after oral use, and in larger amount after intravenous use.

Untoward effects.—Iodides sometimes give rise to certain symptoms either when continued for a long time in large doses or even with small doses due to idiosyncrasy. They are manifestations of irritative phenomena of the skin and the mucous membranes.

Skin.—In escaping through the skin they produce cutaneous eruptions, vesicular, bullous or hæmorrhagic, starting from the papillary layers and not from the sweat glands. All these skin reactions are due to the iodine set free in the skin glands by oxidation. Serious eruptions usually occur in patients with low vitality, and in those with chronic nephritis. Cleanliness of the skin and small doses of arsenic are the best prophylactics known at present.

Mucous membranes.—The mucous membranes of the nose, throat, bronchi, conjunctiva, etc., are irritated by iodides giving rise to symptoms of iodism. There is running of the nose, œdema around the eyelids, sneezing, and headache, the symptoms resembling acute cold or influenza. Sometimes there may be œdema of the glottis with swelling of the parotid glands, a metallic taste in the mouth, loss of appetite, furred tongue, and salivation; while vomiting and diarrhœa may appear in more severe cases. Sometimes the symptoms disappear after the dose is increased, and are more common when the excretion is interfered with as in those suffering from nephritis, and disappear with the stoppage of the drug. The cause of these symptoms is not clearly understood. They are not due to liberation of iodine, nor to anaphylaxis, but are supposed to be due to alteration in the colloid equilibrium (Sollmann). It has been shown that intravenous injection of iodides alters the surface relation of the blood, and that these produce œdema from altered colloid-water affinity.

Antidotes.—Carbonate of ammonium, sp. ammon. aromat., or bicarbonate of potassium controls iodism. Fowler's solution prevents skin eruptions. Calcium lactate is also used.

Therapeutics of Iodides

Internally.—Iodides are employed in the same class of diseases where iodine is indicated but the following deserve a special notice :—

Stomach and liver.—Potassium iodide given after food in

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minute doses, say ½ gr. with aromatic spirit of ammonia or ipecacuanha tincture, is of great service in atonic dyspepsia.

Respiratory passage.—As the iodides liquefy the phlegm and help expectoration, they are used in bronchitis, broncho-pneumonia and pneumonia. Although they have no action on the bronchial muscles they are used in bronchial asthma in 5 to 10 gr. doses, often with benefit. In pleurisy they help absorption of pleuritic fluid. In pulmonary tuberculosis they increase both the cough and expectoration and in some cases may accelerate hæmoptysis. By breaking the tubercular nodules they cause fresh infection by freeing the bacilli.

Heart and circulation.—Iodides are used to absorb the effusion in pericarditis, and the deposits over the valves. They are extremely valuable in all conditions of the heart and the vessels following tertiary manifestations of syphilis. They often give relief to pain of aneurism. Prolonged use sometimes **lowers the blood-pressure**, but as a rule fails unless of syphilitic origin. It is believed that it helps to bring the pressure down by its action on the carotid sinus (page 275) provided there is sclerosis of the sinus. Beneficial results have been obtained in **angina** by giving iodine and iodides intravenously, and by subcutaneous injections of CO_2 : both may be used either alternately or simultaneously. It is a valuable remedy in arterio-sclerosis and Stockman has suggested that the value of this drug is due to production of a large amount of thyroxin.

Brain.—It has been used in hydrocephalus, but only acts as a palliative. In **meningitis** and other cerebral lesions of syphilis, a combination with bromide and mercury is the time-honoured treatment.

Skin.—Many syphilitic cutaneous diseases, such as psoriasis and erythema, are sometimes cured by full doses of iodides.

Scrofula.—The iodides, especially syrupus ferri iodidi, either alone or with cod-liver oil, have a remarkable effect in tuberculosis when the glands are affected.

Syphilis.—Although iodides have no toxic effects on treponema, sodium iodide has given good results in locomotor ataxy given intravenously (1 to 3 grm. in 10 p.c. solution). They are of immense value in tertiary syphilis, or rather in the manifestations of untreated syphilis which go to the tertiary stage. Periostitis, nodes, gummata, syphilitic deposits in the brain and other organs disappear with remarkable rapidity. Success depends upon boldly pushing the drug in doses of 20 to 40 grs. or even 1 dr. three times a day. They sometimes do good in the secondary stage specially when combined with mercury. They have no effect in primary stage, but are efficacious in congenital syphilis.

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Goitre.—Iodine or iodides in small doses (2 grs. daily) sometimes produce good results in simple hypertrophic goitre and have been used both for prevention and treatment. But the patient requires to be constantly watched to prevent the symptoms of hyperthyroidism which may follow if the dose is large and used for a prolonged period. In **Graves' disease** its use has proved beneficial in reducing the metabolic rate prior to partial thyroidectomy.

Large doses are of great value in **actinomycosis** or **sporotrichosis** in 60 to 120 grs. given daily.

Metallic poisons.—Potassium iodide eliminates lead and mercury and other metallic poisons from the system; magnesium sulphate should always be given in these cases in combination with the iodide, otherwise the metallic salt may be reabsorbed from the bowels.

Prescribing hints.—Potassium iodide is best administered freely diluted in water or milk, preferably an hour after food. When taken in this way the chances of iodism are less. While some patients suffer from iodism within a few hours after a relatively small dose, others bear quite large doses. Given soon after meals, it may cause gastric irritation from liberation of iodine, but taken half an hour before meals it is free from this effect. As they are incompatible with too many drugs, iodides should preferably be prescribed alone. They are incompatible with alkaloidal salts, and should not be prescribed with liquor strychnine, which will throw down alkaloidal precipitate. Pot. iodide should not be used with calomel as it forms a highly irritating and toxic iodide of mercury. Acids for the most part decompose iodides setting free iodine. The same is true with hydrogen peroxide. Iodides precipitate heavy metals. When prescribed with ferric salts iodine is liberated, also when combined with spiritus ætheris nitrosi if acid. When combined with subnitrate of bismuth the mixture turns yellow from free iodine and from formation of iodide of bismuth.

Class C: Drugs used in Leishmaniasis

ANTIMONII ET POTASSII TARTRAS

Potassium Antimonyltartrate

Syn.—Antimonium Tartaratum; Tartar Emetic.

Source.—Obtained by the interaction of antimonious oxide and potassium acid tartrate. Contains not less than 99 p.c. postassium antimonyl tartrate.

Characters.—Colourless, transparent crystals, or a white, granular powder; efflorescent; taste, sweet, no odour. *Soluble* in 17 parts of water, in 3 parts of boiling water, insoluble in alcohol (90 p.c.).

B.P. Dose.—$\frac{1}{12}$ to $\frac{1}{8}$ gr. or 0.002 to 0.008 grm. *Emetic.*—$\frac{1}{2}$ to 1 gr. or 0.03 to 0.06 grm. *Intravenously.*—$\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.

Note.—Solution for injection may be sterilised by heating in an autoclave, by tyndallisation, or by filtration.

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ANTIMONII ET SODII TARTRAS

Sodium Antimonyltartrate

Source.—May be obtained by the interaction of antimonious oxide and sodium acid tartrate.

Characters.—Colourless and transparent, or whitish, scales or powder. No odour; taste, sweetish. Hygroscopic. *Soluble* in 15 parts of water, insoluble in alcohol (90 p.c.).

B. P. Dose.—$\frac{1}{32}$ to $\frac{1}{8}$ gr. or 0.002 to 0.008 grm. *Emetic.*—$\frac{1}{2}$ to 1 gr. or 0.03 to 0.06 grm. *Intravenously.*—$\frac{1}{2}$ to 2 grs. or 0.03 to 0.12 grm.

Non-official Preparations

1. **Vinum Antimoniale.**—Tartarated antimony 4 grm., boiling water ·4 mils., sherry *q.s.* to 1000 mils. *Dose.*—10 to 30 ms. or 0.6 to 2 mils.

2. **Stibenyl.**—Sodium acetyl-p-aminophenyl stibinate.—A brownish powder, soluble 1 in 10 parts of water. Can be given intramuscularly. Results have not been encouraging. Analogous to *arsacetin*. *Dose.*—$\frac{3}{4}$ to 1$\frac{1}{2}$ gr. or or 0.05 to 0.1 grm. intravenously in 30 c.c. of water.

3. **Urea Stibamine.**—A compound of urea and *p*-amino-phenylstibinic acid. Gives good results in the treatment of kala-azar with injections of 0.05 to 0.3 gm. in 2 p.c. solution twice a week intravenously.

4. **Stibosan.** *Syn.*—*Von Heyden* 471.—It is a sodium salt of m-chlor-p-acetyl-aminophenyl stibinic acid. Useful in kala-azar. *Dose.*—0·15 grm. initial dose and 0.3 grm. subsequently. Solutions should not be boiled and should be prepared fresh to make a 5 p.c. solution. A stable compound and does not undergo any change when exposed to air.

5. **Neostibosan.** *Syn.*—*Von Heyden* 693 B.—It is diethylamine para aminophenyl-stibinic acid. *Can be given intramuscularly.* 0.3 grm. in distilled water to make 25 p.c. solution. Eight daily injections are given. The total quantity being 2.5 gm. The first dose is 0.2 grm.

Pharmacology

Externally.—Salts of antimony are powerful **irritants** to the skin and form characteristic local lesions, first papular, then vesicular and lastly pustular. These rashes resemble small pox and are due to the formation of insoluble irritant precipitates at the orifices of the sweat glands by the acid perspiration. The pustules sometimes coalesce and form a big ulcer which on healing leaves an unsightly scar.

Internally.—In the stomach antimony has the same irritant action as observed on the skin, but the degree of irritation depends upon the amount used. In small doses it produces a sense of warmth and soreness, and in larger doses loss of appetite, nausea and increased secretion of gastro-intestinal mucus. In still larger doses (1 to 2 grs.) it induces **vomiting** which is accompanied by depression, cold perspiration, hurried respiration and increased bronchial and salivary secretion. The vomiting is due to direct irritant action on the stomach, although it was once attributed to stimulation of the centre. The salts dissociate in the stomach and intestine and increase their peristaltic movement. But the antimony ion is slowly absorbed from the stomach, therefore the effects are entirely confined to the stomach, and since most of it is expelled out very little enters the intestine, unless a large quantity is used, or more passes into the

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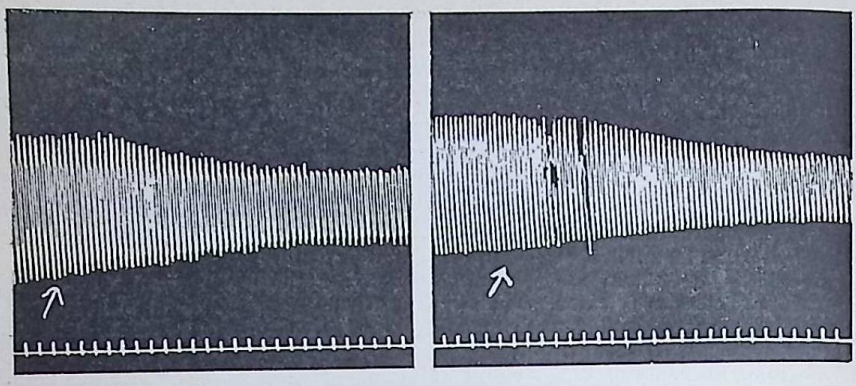
intestine than is expelled out by the vomit. In toxic doses it is a powerful **gastro-intestinal irritant** like arsenic.



A B

Fig. 13.—Perfusion of isolated Heart of Guinea-pig. A. Showing the effect of sodium antimony tartrate (0.5 c.c. of 1 p.c. solution). B. Effect of potassium antimony tartrate (0·5 c.c. of 1 p.c. solution). Note weakening and slowing of the heart.

Heart and circulation.—From the beginning, even in small doses, antimony reduces the force and frequency of the cardiac beat which tends to become intermittent, and in large doses the heart becomes profoundly depressed with acceleration of the pulse-rate. The blood-pressure falls considerably (1) partly from the depressed condition of the heart, (2) partly from the relaxed state of the arterioles caused by the depression of some portion of the vaso-motor system, and (3) partly reflexly from the stomach (nausea). Hence, antimony is a powerful cardiac and circulatory depressant. Antimony probably circulates in the blood in combination with proteins. It increases the number of leucocytes and is said to diminish the red blood-cells.

Respiration.—Respiration is very much depressed after a brief stimulation. Inspiration becomes short, expiration prolonged, and finally respiratory movements become irregular. In fatal poisoning the lungs become congested. It increases the bronchial secretion and helps expectoration. This effect is chiefly reflex from gastric irritation.

Temperature is not much affected in health but is reduced in fevers, owing chiefly to diaphoresis, caused by (1) the depressed condition of the circulation, (2) dilatation of peripheral vessels, and (3) possibly to some extent from gastro-enteritis.

Nervous system.—The cerebrum is depressed causing a feeling of languor, inaptitude for mental exertion, lowness of spirits and sleepiness. These effects are indirect through circulatory depression and disturbances of the gastro-intestinal tract.

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Metabolism.—Its effects on metabolism are much the same as those of phosphorus and arsenic. Continued long it causes fatty degeneration of many organs specially the liver. The glycogen may disappear from the liver, and there is increased elimination of nitrogen and deficient oxidation of tissues.

Micro-organisms.—Like arsenic, antimony in dilutions of 1 in 200,000 kills **typanosomes**, and the trivalent antimony, whether in organic or inorganic combinations, is more toxic than the pentavalent form. Antimony therefore has a specific action on trypanosome in much the same way as quinine on the malarial parasite. In fact Cushny has shown that in dilutions of 1 in 500,000 it has a destructive action on trypanosome in the blood. On the other hand Noguchi has pointed out that the highest dilution of tartar emetic lethal to cultures of leishmania is 1 in 100 *in vitro*, and that its action is not increased by contact with fresh animal tissue. In the body its concentration is not likely to be greater at any time than 1 in 10,000. Moreover pentavalent compounds are excreted more rapidly than trivalent derivatives. In fact Brahmachari has shown that 30 to 40 p.c. of urea stibamine is excreted within 24 hours after injection, whereas only 6 p.c. of tartrate is excreted in the same period. It is evident therefore that antimony by itself cannot cure kala-azar, and it has been suggested that either it forms a new compound with the tissues of the host which exerts a parasiticidal effect, or that it liberates from the tissues immune bodies which destroy the parasites.

Elimination.—Absorption of antimony is slow, the salts are excreted by the kidneys, bile, skin, mucous membranes of the bronchi, gastro-intestinal tract and mammary glands. A portion is stored up in the liver. A considerable amount is excreted by the intestine, a large portion is also thrown out by the kidneys.

Toleration.—Large doses given several times a day sometimes do not induce vomiting, thereby producing tolerance of the drug.

Acute toxic action is very much the same as that of arsenic. Pain and discomfort in the region of the stomach, headache, general weakness, profuse diarrhœa and jaundice are some of the symptoms. Albumin appears in the urine and the pulse becomes slow and weak. The *post mortem* appearances are not so marked as in arsenical poisoning.

Antidotes.—Emetics or stomach-pump if vomiting is not free. *Tannin is the chief antidote* in any shape. Strong tea, coffee, gallic acid, astringent infusions, and demulcent drinks should be freely given. Stimulants, strychnine subcutaneously. *Chronic toxic action* is rare nowadays.

THERAPEUTICS

Externally.—As a *counter-irritant*, tartarated antimony ointment (5 p.c.) is used in cases of **kala-azar** of children who cannot be given intravenous injections. Application of 1 to

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2 p.c. tartar emetic ointment has given good results in the treatment of **oriental sores.**

Internally. **Gastro-intestinal tract.**—As an *emetic,* tartar emetic is not suitable in cases of poisoning on account of its tardy action and the general prostration it induces, but is of great service in those cases of acute inflammatory affections of the respiratory tract, such as **croup** and **bronchitis** where both emesis and vascular depression are needed. Formerly antimony was used largely in acute inflammatory fevers, but its use has now been given up. It is only used in cases of bronchial affections of children in combination with ipecacuanha tincture.

It is chiefly used in the treatment of several tropical diseases, such as leishmaniasis, trypanosomiasis, yaws and bilharziasis. It has also been used in malaria and filariasis, but the results have not been encouraging.

The treatment of leishmaniasis with antimony preparations constitutes one of the most important advances in chemotherapy. The best results are obtained when the treatment is commenced early. In fact 18 to 25 injections of tartar emetic or sodium antimonyltartrate spread over two to three months will effect complete recovery. The routine method is to give these injections intravenously, commencing with 0.5 c.c. of a 2 p.c. solution and gradually increasing the dose by the same amount each week till a maximum of 4 to 5 c.c. is reached. These injections can be given every 2 or 3 days as long as no toxic symptoms or any excessive reaction occur. Some prefer 1 p.c. solution. The solution can be sterilised by boiling. If any fluid escapes into the tissues around the vein there will be pain and inflammatory induration. According to Napier the maximum curative dose of tartrate is 4 grm. for every 100 pound of body weight. In practice however a maximum of 2.52 grm. in 30 injections is sufficient. For children or debilitated patients the initial dose should be 0·25 c.c. Children tolerate relatively larger doses than adults.

The success of the antimony treatment has led to the introduction of many preparations, but Urea Stibamine of Brahmachari, gives the best results, and cases resistant to tartrates or other preparations recover under its use. Although it is claimed by some workers that Neostibosan is superior to many other preparations inasmuch as it effects a cure with eight daily injections, the results have not been so brilliant as anticipated, and it has no advantage except that it can be given intramuscularly.

Owing to the toxicity of the potassium salt, sodium tartrate of antimony is preferred by many in the treatment of **bilharziasis.** Quite recently a trivalent antimony compound of pyrocatechin sodium disulphonate (**Fuadin**) has been used. The injections are given into the gluteal muscle. The

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usual dose is 1·5 c.c. of a 7 p.c. solution on the first day, 3.5 c.c. on the second day, and 5 c.c. on the third day, after which the same dose is given on alternate days till the fifteenth day. 5 c.c. contains 42.5 mgm. of antimony. It has also given good results in *granuloma inguinale* when used in the same way as for bilharziasis.

Toxic symptoms associated with intravenous injections.—As a rule no untoward symptoms are noticed in the majority of cases provided the treatment is commenced with small doses and gradually worked up to the maximum dose. A certain number of patients however show an intolerance to the drug, and untoward symptoms may appear even after very moderate doses. These symptoms may be classified as follows: (*a*) Gastro-intestinal symptoms. Severe fits of coughing and retching immediately after an injection is very common. These are less likely to occur if the injections are given on an empty stomach. Nausea and vomiting and sometimes acute diarrhœa may follow an injection. (*b*) A slight rise of temperature with or without rigor; this is of no significance unless excessive. (*c*) Cyanosis, rapid and irregular pulse. (*d*) Nervous symptoms. General depression when the treament has been continued long, persistent headache and hemicrania. Rarely loss of consciousness and incontinence of urine and fæces. (*e*) Pain on the shoulders and in the big joints. (*f*) Papular eruptions. (*g*) Symptoms suggestive of acute hepatitis with jaundice and recurrence of fever. (*h*) Anaphylactic-like syndrome. Generally occurs suddenly after the 6th or 7th injection. Face becomes puffy, urticarial rashes appear all over the body, and difficulty of breathing. In severe cases pulse becomes imperceptible and collapse sets in with stertorous breathing and unconsciousness. These symptoms disappear soon. Though alarming no deaths have been reported.

Appearance of any of these symptoms demands either reduction of the dose or stoppage of treatment.

Prescribing hints.—The use of antimony in the treatment of kala-azar is almost universal and the student should know its different methods of administration. In cases of children, or where its use is otherwise contra-indicated, tartar emetic ointment 5 p.c. or metallic antimony 5 to 10 p.c. in lanoline may be rubbed on the skin. Only small doses can be given by the mouth, and therefore in the treatment of protozoal diseases where stronger concentration is required this method is of no use. Intramuscular injections are very irritating and painful, producing severe inflammation. Although several preparations are now available which are claimed to have the advantage of not producing any local effect, the intravenous route is the only reliable method and should always be adopted. Some patients are intolerant to even small doses of antimony.

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Class D : Drugs used in Trypanosomiasis

These include pentavalent arsenic compounds, *viz.* **Cacodylates** (*see* page 472), **Atoxyl, Tryparsamide, Fourneau, Bayer 205.**

Sodii para-aminophenylarsonas. *Syn.—Atoxyl ; Soamin.*—Both soamin and atoxyl which are closely allied preparations were first tried in the treatment of **sleeping sickness**; the former more extensively than the latter. They both cause the trypanosomes to disappear from the peripheral blood for long periods. They were however found to be of little value in the sleeping stage as they do not penetrate the meninges.

A number of cases of recovery in the early stages have been recorded by different observers. The method of treatment is to give injections of either soamin or atoxyl in 10 p.c. solution once a week. The usual dose being 3 to 7 grs., commencing with 3 grs. and then working up to 7 grs. The only disadvantage is that it may cause dimness of vision and optic atrophy. The sight therefore requires to be tested during the course of treatment and any restriction in the field of vision necessitates either stoppage of the treatment or reduction of the dose. The routine method is either to give the injection every 5 or 6 days, or once a week for a month, or till 100 grs. have been given and then to wait for one month before another course is given. This is continued for at least one year after all signs of the disease have disappeared. (*See* also page 473).

Tryparsamide.—Recently this preparation has been introduced which promises to give better result. It causes disappearance of the human trypanosomes from the peripheral blood, specially the *Gambiense* infections. The usual dose is 0.3 to 7.0 grm. in 10 p.c. solution intramuscularly or intravenously. During the second stage, with nervous symptoms, it produces marked improvement in the cell content of the cerebrospinal fluid with arrest of the symptoms, in doses of 3 to 5 grm. Only disadvantage is that it also causes transient dimness of vision. F. van den Branden and his colleagues, in the Belgian Congo advise a total 20 to 40 grms. in early cases, and 50 to 100 grms. in chronic ones, in doses of 3 grms., and 0.5 to 2 grm. in children. (*See* also page 473).

Fourneau 270, or *Orsamine* is the sodium salt of acetyl-*p*-amino-oxyphenyl-aresnic acid. In white powder. It is used in freshly prepared solution in doses gradually increased from 1 to 6 grm. per kilo of body weight. The injections are given subcutaneously or intravenously in 20 p.c. solution. Good results have been recorded in the first and second stage.

Bayer 205, or *Moranyl ; Germanin.*—A white amorphous powder, freely soluble in water and saline solution forming a neutral solution. Its composition is not known, probably belongs to the trypan red class of dyes. *Dose.*—0.6 to 1 grm. in 10 p.c. solution intravenously or intramuscularly every 2 to 6 days up to 5 injections.

Action and Uses.—Its action in this disease was established by giving injections of the drug to infected small animals chiefly mice ; and it has since been extensively used on human beings. The results were not very encouraging except in infections with *T. rhodesiense.* It is however more effective in early cases before the cerebrospinal fluid is infected. As a prophylactic it has been found rather effective, giving protection for seven months. Its use is generally supplemented by the administration of tryparsamide, but it has been found that this increases the danger to sight of tryparsamide.

The drug is very expensive and produces toxic effects on the kidneys which precludes its further use.

Class E : Amœbicidal remedies

These include **Ipecacuanha** and its alkaloids (*see* page 297), **Stovarsol, Carbarsone, Vioform, Yatren, Rivanol**

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Stovarsol (*see* page 473).—It has been used with certain amount of success in chronic amœbic dysentery specially in the resisting cyst-passing cases. It is generally given by the mouth in 4 gr. doses twice a day. It is also taken after a course of emetine to prevent relapses, but often fails to prevent this. Its only disadvantage is that it has a tendency to induce severe dermatitis. A few cases of deaths after stovarsol are on record and therefore it should be used with caution.

Carbarsone.—4-carbaminol-phenyl arsonic acid. Contains 28.8 p.c. arsenic. It is extolled as a valuable remedy in amœbic dysentery and is non-toxic. It is administered by the mouth in 0·25 grm. or $3\frac{3}{4}$ gr. doses in capsules twice a day for 10 days. In obstinate cases an enema of 2 grm. in 200 c.c. of warm 1 p.c. sodium bicarbonate solution is instilled into the rectum after a cleansing enema, and repeated every alternate night for five nights.

It is contra-indicated where the kidneys and the liver are damaged.

Vioform.—Iodochlor-hydroxy-quinoline. A greyish-yellow powder almost insoluble in water and sparingly soluble in alcohol. Contains 40 p.c. iodine.

Dose.—0.25 grm. or $3\frac{3}{4}$ gr. in capsules for ten days. The course being repeated after a week's rest. Total quantity being 15 grm.

It has been used in amœbiasis with much success.

Yatren. *Syn.*— *Quinoxyl ; Loretin.*—Sodium Iodohydroxy-quinoline Sulphonate. A pale yellow hygroscopic powder. Contains 28 p.c. iodine. In acute and chronic amœbic dysentery. Useful also in bacillary dysentery and lamblial cysts.

Dose.—5 to 15 grs in pills or powder.

Rivanol. *Syn.—Ethoxy-diamino-acridine Lactate.*—A yellow dye stuff with powerful antiseptic action. Useful in human amœbiasis, bacillary dysentery and acute and chronic enteritis of adults and children.

Dose.—0.025 grm. or $\frac{2}{5}$ gr. for adults ; 0.008 grm. or $\frac{1}{8}$ gr. for children, 3 to 4 times a day. May also be used as enema, 10 to 20 oz. of 1 in 5000 to 1 in 3000 solution injected slowly.

GROUP XVII

VOLATILE OILS

General Action of Volatile Oils

Micro-organisms.—The volatile oils are **antiseptics,** both when used externally and also when taken internally. Some are more powerful in this respect and these belong chiefly to the turpentine group, and the empyreumatic oils are largely used as efficient antiseptics and disinfectants. This action depends upon their volatility and solubility in lipoids which enable them to enter the bacteria more easily. The only drawback is their insolubility in water.

Skin.—Applied to the unbroken skin they first stimulate then depress the local sensory nerves and produce irritation and itching followed by numbness. The irritation is accompanied by redness caused by dilatation of local blood vessels. Volatile oils are therefore **irritants, rubefacients** and **mild anæsthetics.** Some of them, *e.g.*, turpentine, rosemary, cajuput, mustard, etc., are powerful irritants and counter-irritants. Others again affect in a specific manner the nerve

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endings conveying the sensation of cold. To this class belongs the stearoptenes, particularly menthol.

Alimentary canal.—The same irritant effect is observed in the mouth and stomach. Taken freely diluted, as in the form of aromatic waters, they stimulate the nerves of taste and produce a sensation of heat in the mouth and reflexly induce salivary and gastric secretions. In the stomach volatile oils are mild irritants and cause a sense of heat in the epigastrium and provoke appetite for food. They stimulate the gastric mucous membrane, increase its vascularity, accelerate the secretion, and give rise to eructation and expulsion of gas from relaxation of the sphincters. They are **stomachics, carminatives** and **mild antiseptics.** In concentrated form, or the more powerful ones, may give rise to gastro-enteritis with hiccough, vomiting and diarrhœa. The milder ones, viz. anise, dill, cinnamon, peppermint, etc., are largely used as carminatives and flavouring agents. Lower down in the intestine they increase their movements in small doses, while large doses decrease them. Clinically their use is followed by expulsion of gas and relief of colic, and they are largely used with purgatives. Some are **anthelmintics,** *e.g.*, thymol, oils of chenopodium and turpentine.

Nervous system.—In ordinary therapeutic doses the effect on the nervous system is purely reflex from the mouth and the stomach. The vessels of the skin dilate and there is a feeling of warmth and relief of chill. The vaso-motor, accelerator and the respiratory centres are stimulated causing a rise of blood-pressure, acceleration of respiration, and a feeling of general well-being. The nervous system is affected directly only in large doses. The cerebrum is first stimulated and then depressed, but this differs in different preparations. Turpentine causes less excitement but more drowsiness, whereas camphor stimulates and produces cerebral excitement and convulsion.

Volatile oils are rapidly absorbed both from the stomach and intestine and are eliminated through the different secretions. They can be detected in the breath, urine and sweat, to which they impart their characteristic odour. They are excreted with the urine in combination with glycuronic acid and during excretion stimulate the renal cells and act as **diuretics.** Some, like sandal wood oil, copaiba, cubebs, buchu, etc., are powerful **genito-urinary antiseptics.** While excreted through the bronchial mucous membrane they stimulate the secretions of the bronchial glands and act as **expectorants** and **pulmonary antiseptics.** Some are extensively used as such but their value as antiseptic to the respiratory tract when used by the mouth is doubtful.

They circulate in the blood unchanged and cause **leucocytosis,** the polynuclear variety being mostly increased.

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This effect is due to their irritant action on the alimentary canal.

The volatile oils are classified as follows :—

Class A : Turpentine Group
1. Oils : **Oil of Turpentine, Oil of Pine** (Abietis)
2. Resins and Oleoresins : **Colophony, Myrrh, Storax, Balsam of Peru, Balsam of Tolu**
3. Empyreumatic Oils : **Tar, Coal Tar** (*see* antiseptics), **Oil of Cade**

Class B : Volatile Oils having Special Stimulating Effect on the Skin
Oil of Eucalyptus, Oil of Cajuput, Oil of Rosemary, Oil of Mustard, Capsicum

Class C : Genito-urinary Antiseptics and Diuretics
Copaiba (*see* page 386), **Oil of Sandal Wood** (*see* page 388), **Buchu** (*see* page 389)

Class D : Nauseants
Asafetida, Valerian

Class E : Carminatives and Flavouring Agents
Cloves, Cardamoms, Caraway, Coriander, Anethi, Anise, Lemon, Fennel, Cinnamon, Nutmeg, Oil of Lavender, Peppermint, Ginger

Class A : Turpentine Group

OLEUM TEREBINTHINAE

Oil of Turpentine

Syn.—Rectified oil of Turpentine.

Source.—An oil distilled from the oleo-resin (turpentine), obtained from various species of *Pinus*, and rectified.

Characters.—Limpid, colourless, liquid. Characteristic odour and a pungent, bitter taste. Sp. gr. 0.860 to 0.870. *Solubility.*—Insoluble in water ; soluble 1 in 7 of alcohol (90 p. c.) and in all proportions of ether, chloroform, and glacial acetic acid.

Composition.—Two isomeric bodies *d*-and *l*-pinene. Other constituents are *resin acids*, *camphene* and *fenchene*. *Dipentene* and polymeric *terpene* may also occur. Formic, acetic and camphoric acids and camphoric aldehyde.

B.P. Dose.—3 to 10 ms. or 0.2 to 0.6 mil ; as an anthelmintic—120 to 240 ms. or 8 to 16 mils.

Official Preparations

1. **Linimentum Terebinthinæ.**—65 p. c.
2. **Linimentum Terebinthinæ Aceticum.**—44.5 p.c.

Non-official Preparations

1. **Terpini Hydras, U. S.** *Syn.—Terpine Hydrate.*—A hydrate of the dihydric alcohol. Colourless, lustrous crystals or a white powder. Efflorescent; action similar to turpentine, but less disagreeable and less toxic. Diminishes cough and expectoration. Used in *bronchitis, phthisis, hæmoptysis. Dose, U. S. P.*—0.25 grm. or 4 grs.
2. **Terpinol, B.P.C.**—A mixture of several terpenes. An agreeable aromatic liquid. In *chronic bronchitis* and *phthisis. Dose.*—1 to 2 ms. or 0.06 to 0.12 mil, given during meals.

Pharmacology

Externally.—When rubbed into the skin, it is a rubefacient, irritant, and counter-irritant, and later on a local

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anæsthetic. In large amounts it is a vesicant. It is also a local antiseptic and disinfectant, and it is absorbed by the unbroken skin.

Internally. **Gastro-intestinal tract.**—The same action is observed when taken internally, *i.e.*, it dilates the gastric vessels, and increases both the peristaltic movements and the secretion of gastric juice; at the same time it reflexly stimulates the heart, but on account of its sickening taste it is never used for this purpose as other volatile oils act equally well and are not so nasty. In the intestine it helps expulsion of flatus and is a strong carminative. In large doses it causes great vascular dilatation and purging, the stools containing large quantities of blood. In doses of 2 to 4 drs. it is an anthelmintic for tapeworm, but this treatment is too dangerous for adoption. As an enema it kills thread-worms.

Circulation.—The reflex effect on the heart has already been alluded to. It circulates as turpentine and causes a rise of blood-pressure from stimulation of the vaso-motor centre. In large doses the pressure falls from paralysis of the centre causing dilatation of the vessels and depression of the heart. It causes contraction of the small vessels, and since it causes clotting of the blood when locally applied it is a hæmostatic.

Respiration.—When inhaled it produces sneezing, a tight feeling across the eyes and dyspnœa, due to reflex irritation from the action on the nasal mucous membrane. It directly irritates the bronchial mucous membrane, causing dilatation of the vessels, increase of the secretion, and stimulation of the muscular coats of the bronchi, whilst reflexly it excites cough. At the same time it increases the activity of the respiratory movements, and is a **powerful expectorant.** If the secretion is purulent it is disinfected. When taken internally, turpentine is excreted by the bronchial mucous membrane, and has a similar action to that already described.

Nervous system.—Large doses cause languor, hebetude, drowsiness and unsteadiness of gait. Toxic doses are followed by coma and paralysis of the sensory nerves with abolition of reflex action.

Kidneys.—Here its action is specially powerful. The renal vessels are dilated causing some diuresis. It appears in the urine in combination with glycuronic acid. Comparatively small doses may cause lumbar pain, scanty urine, albuminuria and hæmaturia, with all the symptoms of strangury. After a large dose there may even be complete suppression of urine. The urine has a smell of violets.

Skin.—It is excreted by the skin and sometimes causes erythema.

THERAPEUTICS

Externally.—Turpentine *stupes* (flannels wrung out of very hot water and sprinkled with turpentine) are largely used to

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produce irritant or **counter-irritant** effects in various forms of acute and chronic inflammation, such as pleurisy and bronchitis. The liniments are valuable applications to painful areas, as in neuralgia, myalgia, rheumatism, lumbago, and unbroken chilblains. Pure turpentine has been used as a **parasiticide** in the various forms of tinea. Turpentine may also be used for the cure of psoriasis in cases where chrysophanic acid causes too much irritation. For this purpose the scales must first be removed by alkaline baths, and then a mixture of turpentine and olive oil (1 in 4) painted on. Afterwards gradually increase the proportion till the pure oil is used. On account of its property of constricting the vessels, turpentine is used as a **hæmostatic** to check the free oozing that follows removal of the jaw, excision of the tongue, and many operations about the mouth, in which cases its antiseptic properties are also of value. The vapour also checks the bleeding in hæmoptysis but the air of the patient's room must be saturated with it.

Internally. **Gastro-intestinal tract.**—In large doses (15 to 30 ms. every hour for a few hours) it is a **hæmostatic** in gastric ulcer and typhoid fever; whilst as an enema it relieves tympanitic distension of the abdomen.

Respiratory tract.—It is not much used as an inhalation, as pumiline, terebene, and eucalyptus oil are much more pleasant and less irritating. Given internally in small doses it is useful in chronic bronchitis, but terpine hydrate and terpinol are to be preferred.

It may be used as a diuretic, but since it irritates the kidneys, it should be used with caution. For the same reason its use as internal hæmostatic has been given up and is perhaps of little value.

Caution.—Turpentine must always be given cautiously on account of its liability to set up strangury, and *it should never be given at all to subjects of Bright's disease* as in cases of this kind it may cause fatal suppression of urine.

TEREBENUM

Terebene

Source.—Obtained by steam-distilling the product of the limited action of sulphuric acid on oil of turpentine.

Characters.—A colourless, or pale-yellow liquid, with a pleasant and characteristic odour; taste, aromatic, terebinthinate. *Sp. gr.* 0.862 to 0.870. Almost *insoluble* in water, miscible with dehydrated alcohol.

Composition.—A mixture of *dipentene* and other hydrocarbons.

B. P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

Non-official Preparation

1. **Vapour Terebenæ, T.H.**—Terebene 40 ms., Magnesii Carbonas Levis 20 grs., Water to 1 oz. A teaspoonful of this in a pint of water at 140°F. as an inhalation.

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Pharmacology and Therapeutics

As an *expectorant*, it has been given with success in chronic bronchitis, winter cough and phthisis, especially when complicated with emphysema. It may be exhibited in various ways: (*a*) *Externally*, either as an inhalation in the form of the vapour, or 15 to 30 drops may be sprinkled on the cotton-wool of an antiseptic respirator, or it may be used as a spray; (*b*) *Internally*, as a mixture, either alone or combined with apomorphine and other expectorants: or five drops may be taken a few times a day on a lump of sugar, or in capsules or thick syrup.

As an *antiseptic* and *sedative*, the vapour of terebene is useful in phthisis, in which disease it is usual to combine it with equal parts of phenol and thymol, or phenol and spirit of chloroform, and use 10 drops of this mixture for medicating the antiseptic respirator. Terebene acts on the mucous membrane of the urinary and gastro-intestinal tract in much the same way as turpentine.

Prescribing hints.—Terebene must be given with caution to gouty patients, and to subjects of chronic kidney troubles, as it may increase the albuminuria in cases of this kind.

OLEUM ABIETIS

Oil of Siberian Fir

Syn.—Oil of Pine; Pinol; Pumiline.

Source.—The oil distilled from the fresh leaves of *Abies sibirica*. Contains from 35 to 40 p.c. w/w of esters, calculated as bornyl acetate.

Characters.—Colourless or nearly so. Odour, pleasant, aromatic. Taste, pungent. Sp. gr. 0.905 to 0.925.

Composition.—Contains bornyl acetate 45 p.c. *Pinene*, *camphene*, *dipentene* and *phellandrene*.

Non-official Preparations

1. **Syrupus Pini, B.P.C.**—Pine Oil 0·62, Comp. solution of Tartrazine 1, Alcohol (90 p.c.) 12.50, Glycerin 25, Sucrose and Water to 100. *Dose.*—30 to 60 ms. or 2 to 4 mils.

2. **Linctus Pini, Terpin et Heroin.**—Contains Heroin Hydrochlor. 1/48 gr. and Terpin Hydrate 1/4 gr. to each drachm. *Dose.*—30 to 60 ms. or 2 to 4 mils.

Pharmacology and Therapeutics

Externally.—The action and uses of the oil of pine resemble that of the oil of turpentine, it is more pleasant, and is used in bronchitis, phthisis and emphysema. It may be inhaled from a handkerchief or better through an inhaler. *Vapor Olei Pini, B.P.C.* can be made by triturating oil 10 with mag. carb. levis 6, and adding water to 100. Of this 1 dr. is put into an inhaler containing half a pint of cold and half a pint of boiling water.

Internally.—Given internally it is excreted by the bronchial mucous membrane, stimulating and disinfecting its

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secretion, and is therefore useful in bronchitis and chronic wasting lung diseases. It may be taken on sugar or in the form of pastil.

COLOPHONIUM

Colophony

Syn.—Resina ; Resina.

Source.—The residue left after the distillation of the volatile oil from the oleo-resin of various species of *Pinus*.

Characters.—Translucent, light amber-coloured, compact, brittle glassy masses ; fracture, shining ; odour and taste, terebinthinate. *Solubility.*—Freely in alcohol (90 p.c.), ether, benzene, carbon disulphide. Insoluble in water.

Composition.—It is an anhydride of three isomeric *Abietic acids*, traces of a volatile oil, a *resene* and a bitter principle.

Official Preparation

1. **Emplastrum Colophonii.** *Syn.—Adhesive Plaster.*—1 in 10.

Pharmacology and Therapeutics

Externally.—Resin is an antiseptic and mild stimulant, and is therefore useful in indolent ulcers, wounds and sores. Basilicon ointment (colophony 26 p.c., yellow beeswax, lard and olive oil) is an excellent application for this purpose, but is apt to prove too stimulating if used for any length of time. Its chief use now is in pharmacy, to impart consistence and adhesiveness to plasters and ointments.

MYRRHA

Myrrh

Syn. I.V.—*Gandharasha, gandhabol. Bol*, Beng. *Bola*, Sans.

Source.—An oleo-gum-resin obtained from the stem of *Commiphora molmol*, and probably other species *of commiphora*.

Characters.—In rounded or irregular tears, or masses of irregular tears, varying in size ; reddish-brown or reddish-yellow externally, dry, covered with a fine powder ; brittle, fractured surface irregular, somewhat translucent ; brown, oily, with whitish marks. Odour, aromatic. Taste, aromatic, bitter, acrid.

Composition.—(1) *Gum* 57 to 61 p.c. (2) A *resin, myrrhin*, 25 to 40 p.c. (3) *Myrrhol*, a volatile oil, 2.5 to 8 p.c. (4) A bitter principle.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Official Preparation

1. **Tinctura Myrrhæ.**—1 in 5. **B.P. Dose.—30 to 60 ms or 2 to 4 mils**

Pharmacology

Externally.—Like other oleo-resins, locally, myrrh is a mild disinfectant, and stimulant to the ulcerated and mucous surfaces.

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Internally. **Gastro-intestinal tract.**—The same action is noticed in the mouth, throat, stomach and bowels. It promotes appetite, excites gastric secretion and peristalsis of the stomach and intestines, and is therefore a stomachic and carminative.

Blood.—It increases the number of leucocytes, perhaps by stimulating lacteal activity. It stimulates phagocytosis.

Elimination.—It is excreted by the mucous membranes especially those of the respiratory and genito-urinary tracts, which it stimulates and disinfects; hence it is an expectorant, emmenagogue and uterine stimulant.

Therapeutics

Internally.—Myrrh makes a good **mouth-wash** (Tr. Myrrh. 5, Honey 5, Inf. Rosæ to 100) for aphthous and ulcerated tongue, relaxed throat and spongy gums. Its efficacy is increased if combined with borax, as in tr. myrrhæ et boracis. For receded and ulcerated gums, tr. myrrhæ and liquor iodi mitis make a superior preparation. For its stomachic and carminative properties, it is often used as an adjunct of purgatives. As a disinfecting expectorant, it is occasionally given in chronic bronchitis and bronchiectasis. For its emmenagogue property it is largely prescribed in **amenorrhœa**, in conjunction with aloes and iron. Some however doubt its emmenagogue action.

STYRAX

Storax

Syn.—Styrax Præparatus.

Source.—A balsam obtained from the wounded trunk of *Liquidambar orientalis*, purified by solution in alcohol, filtration, and evaporation of the solvent. Contains not less than 30 p.c. of the total balsamic acid.

Characters.—A brown, viscous substance, transparent in thin layers; odour and taste, agreeable and balsamic. Entirely soluble in alcohol (90 p.c.), and ether.

Composition.—Consists of a resin mixed with an oily liquid. The *resin* consists of *storesinol* combined with *cinnamic acid*. The oily liquid consists of *styrol*, *ethyl cinnamate* and styracin.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm.

Enters into.—Tinct. Benzoini Composita.

Pharmacology and Therapeutics

Storax resembles benzoin and the balsams of Peru and tolu in its action. It is a feeble expectorant and has some tonic effect on the mucous membrane of the genito-urinary tract. It is rarely given internally except in the form of Friar's balsam. An ointment (1 in 4) is a parasiticide in **scabies**. Mixed with an equal part or twice its bulk of olive oil, it kills *Sarcoptes hominis* and pediculi, but albuminuria has been known to follow its application.

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BALSAMUM PERUVIANUM

Balsam of Peru

Source.—A viscid balsam exuded from the trunk of *Myroxylon Pereiræ*.

Characters.—A blackish viscid liquid in bulk, reddish-brown, and transparent in thin layers. Free from stickiness or stringiness. Odour, agreeable, balsamic. Taste, acrid. *Solubility.*—Insoluble in water. easily in chloroform, and 1 in 1 of alcohol (90 p.c.), but on addition of more alcohol the mixture becomes turbid.

Composition.—(1) A colourless, oily, aromatic liquid *cinnamein*, 53 to 66 p.c., and a dark resin 28 p.c. The liquid portion consists of benzyl cinnamate and benzoate of benzyl. (2) The resin consists of a resin alcohol with *cinnamic acid* and *benzoic acid*.

B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

Pharmacology and Therapeutics

Externally.—On account of the volatile oil it contains, balsam of Peru is an antiseptic and stimulant to the skin and abraded surfaces, and may be applied to wound, indolent ulcers, bed-sores, etc. An ointment (12½ p.c. in simple ointment) cures sore nipples and cracked lips. It kills pediculi and the acarus scabiei and is more agreeable than sulphur.

Internally.—Like most volatile oils, it is a stimulant and carminative. During its elimination by the bronchial mucous membrane it stimulates and disinfects the bronchial secretion and is therefore used as an expectorant in chronic bronchitis.

BALSAMUM TOLUTANUM

Balsam of Tolu

Source.—Obtained from incisions in the trunk of *Myroxylon Toluifera*. Contains 19 to 25 p.c. of the free balsamic acids, and 35 to 50 p.c. of total balsamic acids.

Characters.—A soft, tenacious solid when imported; hardens on keeping; brittle in cold weather; yellowish-brown and transparent in thin films. Odour, fragrant. Taste, aromatic, slightly acid. *Solubility.*—In alcohol (90 p.c.).

Composition.—(1) *Benzoic acid* 8 p.c. (2) *Cinnamic acid* 12 to 15 p.c. (3) A resin 80 p.c. yielding *tolu-resinotannol*. (4) 7.5 p.c. of an oily liquid consisting of *Benzyl cinnamate* and *Benzyl benzoate*. (5) 1·5 to 3·0 p.c. of a very fragrant volatile oil.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Enters into.—Tr. Benzoin. Co.

Official Preparations

1. **Syrupus Tolutanus.**—2.5 p.c. **B.P. Dose.—30 to 120 ms. or 2 to 8 mils.**
2. **Tinctura Tolutana.**—10 p.c. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Pharmacology and Therapeutics

Internally.—Its action resembles those of balsam of Peru. The syrup is used as a flavouring vehicle for cough mixture. The tincture is a feeble expectorant.

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OLEUM CADINUM

Oil of Cade

Syn.—Juniper Tar Oil.

Source.—An oily liquid, obtained by the destructive distillation of the woody portions of *Juniperus Oxycedrus*.

Characters.—A dark reddish-brown, or nearly black, viscid oily liquid. Odour, empyreumatic. Taste, aromatic, bitter, acrid. Sp. gr. 0.975-1.010. *Solubility.*—Freely in chloroform and ether, partially in cold, almost wholly in hot alcohol (90 p.c.), and slightly in water.

Composition.—*Cadinene*, $C_{15}H_{24}$, a sesquiterpene.

Pharmacology and Therapeutics

Externally.—The oil of cade resembles tar in its action, but has a more pleasant odour. It may be used in chronic inveterate eczema, psoriasis and other skin diseases attended with itching. It is applied in the form of an ointment (25 p.c.) combined with yellow beeswax and yellow soft paraffin, or simple cerate, or in a liquid form (oil of cade 1, soft soap 5, alcohol (90 p.c.) 4).

Class B: Volatile Oils having Special Stimulating Effect on the Skin

OLEUM EUCALYPTI

Oil of Eucalyptus

Source.—The oil distilled from the fresh leaves from various species of *Eucalyptus*, and rectified. Contains not less than 70 p. c. of *Cineole.*

Characters.—Colourless or pale yellow. Odour, aromatic, camphoraceous. Taste, pungent, leaving a sensation of coldness in the mouth. Sp. gr. 0.910 to 0.930. *Solubility.*—1 in 5 of alcohol (70 p.c.).

Composition.—(1) *Eucalyptol* (cineole), a volatile oil. (2) A *terpene* called *phellandrene; butyric* and *valerianic aldehydes.*

B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

EUCALYPTOL

Eucalyptol

Syn.—Cineole.

Source.—It is the anhydride of 1 : 8-terpin or menthan-1 : 8-diol, and may be obtained from oil of eucalyptus. Contains not less than 97.5 p.c. w/w of cineole, $C_{10}H_{18}O$.

Characters.—A colourless liquid; odour, characteristic, aromatic and camphoraceous; taste, pungent and cooling. Sp. gr. 0.928 to 0.930.

B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

Non-official Preparations

1. **Nebula Eucalyptolis Composita, B. P. C.**—Eucalyptol 80 mil, camphor and menthol, each 20 grm., thymol 1 grm., light liquid paraffin, *q. s.* 1000 mil.

2. **Vapour Eucalypti Co., B. P. C.** *Syn.—Anti-catarrhal Salts.*—Phenol and oil of eucalyptus each, 16.50, oil of Siberian fir 8.25 strong solution of iodine 8.25, camphor 16.50, ammoniated alcohol 3400.

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Pharmacology

Externally.—Oil of eucalyptus or eucalyptol is a powerful antiseptic and disinfectant. The old oil is more antiseptic than the new because it is more ozonised. Rubbed into the skin it is less irritant than other volatile oils, but if evaporation be prevented it causes rubefaction and vesication. It is destructive to the lower forms of life.

Internally. **Gastro-intestinal canal.**—In small doses it increases the salivary and gastric secretions, and thus acts as a stomachic. In large doses it produces gastro-intestinal irritation with symptoms of vomiting, diarrhœa and colic.

Circulation.—Like quinine, it stops the amœboid movements and diapedesis of the white blood-corpuscles and contracts the engorged spleen. It possesses also mild antiperiodic and antipyretic properties. In small doses it stimulates the heart and raises the blood-pressure reflexly through the stomach : and in excessively large doses the heart becomes weak and the blood-pressure and temperature fall.

Respiration is slightly stimulated by small doses, and is slowed by large ones. Death occurs from respiratory paralysis.

Nervous system.—Large doses depress the action of the brain, the medulla and the cord, thereby paralysing the reflex action.

Elimination.—Like most of the volatile oils, eucalyptol is eliminated by the kidneys, the skin, and the respiratory and the genito-urinary mucous membranes, all of which it stimulates in the course of its passage. Hence it is a diuretic, diaphoretic, a stimulating expectorant, and a disinfecting stimulant to the genito-urinary tract. Like oil of turpentine it causes renal congestion and imparts to the urine an odour like that of violets.

Therapeutics

Externally.—Oil of eucalyptus, though a valuable antiseptic, cannot be freely used on account of its local irritant property and cost. However, the ointment may be used for foul ulcers and wounds. The gauze, lint and wool are often used as antiseptic surgical dressings. Alone or mixed with mustard oil or olive oil it may be rubbed into the skin in chronic rheumatism and myalgia. The vapour (60 drops of eucalyptol in hot water) has been used as an inhalation in pulmonary gangrene, phthisis, chronic or foul bronchitis, etc. Many treat patients suffering from exanthemata, whooping cough and diphtheria by enveloping them in an atmosphere of eucalyptus vapour.

Internally.—To correct fetor of the expectoration or to cut short an attack of coryza, influenza, or catarrh, it may be used with benefit (5 to 10 drops of eucalyptol on sugar). It

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may arrest ague and reduce enlarged spleen, but it is far inferior to quinine. As a stomachic and carminative it has occasionally been prescribed in dyspepsia. A rectal injection of eucalyptol is considered to be an effective remedy for thread-worms.

OLEUM CAJUPUTI

Oil of Cajuput

Syn. I.V.—*Kayaputir tel*, Beng. *Kayaputi ke tel*, Hind., Bom.

Source.—Distilled from the fresh leaves and twigs of *Melaleuca Leucadendron*, and other species of *Melaleuca* and rectified by steam distillation.

Characters.—Colourless or yellow liquid; odour, agreeable camphoraceous; taste, aromatic, bitter camphoraceous. Sp. gr. 0.916 to 0.926. Colourless when rectified. *Solubility.*—In alcohol (90 p.c.).

Composition.—(1) *Cineole* $C_{10}H_{18}O$, 50 to 60 p.c. (2) A crystalline *terpineol; l-pinene;* several *aldehydes.*

B.P. Dose.—1 to 3 ms. or 0.06 to 0·2 mil.

Official Preparation

1. **Spiritus Cajuputi.**—1 in 10. **B.P. Dose.—5 to 30 ms. or 0·3 to 2 mils.**

Pharmacology and Therapeutics

Externally.—It is used as a gentle counter-irritant on the chest in bronchitis, pneumonia, etc; and over painful and chronically inflamed joints. It may be mixed with mustard oil or other stimulating and anodyne liniments.

Internally.—It is a powerful diffusible stimulant, carminative and antispasmodic. It is an excellent remedy for flatulent colic or intestinal spasm, sometimes relieving the pain by a single dose of 20 ms. of the alcoholic solution. For repeated administration an excellent combination is oil of cajuput 2 ms., thymol and menthol each $\frac{1}{2}$ gr., chloroform pure 1 m., oleo-resin of capsicum 1 gr., in keratin-coated capsules.

Prescribing hints.—It may be given on sugar, in sherry, or in the form of an emulsion or pill.

OLEUM ROSMARINI

Oil of Rosemary

Source.—The oil distilled from the flowering plant of *Rosmarinus officinalis.* Contains not less than 2 p.c. w/w of esters, calculated as *bornyl acetate*, and not less than 9 p.c. w/w free alcohols, calculated as *borneol.*

Characters.—Colourless or pale yellow; odour of rosemary; taste, warm, camphoraceous. Sp. gr. 0.900 to 0.912. *Solubility.*—1 in 1 of alcohol (60 p.c.).

Composition.—(1) *Borneol.* 8 to 16 p.c. (2) *Bornyl acetate* and other esters, about 2 to 5 p.c. Camphor, cineole, pinene and camphene.

B.P. Dose.—1 to 3 ms. or 0.06 to 0·2 mil.

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Pharmacology and Therapeutics

Externally.—It is a stimulant and rubefacient to the skin, and is commonly used in the form of hair oil or hair wash, to promote the growth of hair on the scalp in baldness. It is combined with liniments for its odour. Whitla recommends the following as a valuable application in baldness:—Olei rosmarini dr. 4, liquor epispastici dr. 2, ol. amygdalæ dulcis oz. $1\frac{1}{2}$, spt. camph. oz. 2, glycerinum borici oz. 1, oleum rosæ m. 8, tr. jaborandi oz. 1, mix. A little to be rubbed into the roots of the hair every night. It is rarely used internally.

OLEUM SINAPIS VOLATILE

Volatile Oil of Mustard. (Not official)

Source.—The volatile oil distilled from *black* mustard seeds, deprived of most of their fixed oil and macerated in water for several hours.

Characters.—Colourless or pale yellow, intensely pungent and irritant with an acrid taste.

Composition.—Contains glucoside *sinigrin* and an enzyme *myrosin*. In presence of water sinigrin is hydrolysed by the enzyme forming *allyl isothiocyanate*, C_3H_5NCS, also contains *allyl cyanide*, *carbon disulphide* and traces of *isomeric allyl thiocyanate*.

Non-official Preparations

1. **Linimentum Sinapis, B.P.C.**—Volatile oil of mustard 35 ml., camphor 55 grm., castor oil 125 ml., alcohol (90 p.c.) to 1000 ml.

2. **Thiosinamina.** *Syn.—Rhodallin; Allylthiourea.*—Colourless crystals of slight garlic odour and bitter taste. Formed by warming oil of mustard with alcoholic solution of ammonia. Soluble in water, alcohol and ether. 15 to 20 p.c. solution used hypodermically for *lupus*. *Dose.*—$\frac{1}{2}$ gr. to $1\frac{1}{2}$ grs. or 0·03 to 0·1 grm.

3. **Injectio Thiosinaminæ et Sodii Salicylatis.**—Consists of thiosinamin 10 p.c., and sodium salicylate 5 p.c. *Dose.*—8 to 15 ms. or 0·5 to 1 mil. every two or three days: 1 c.c. contains approximately 1 gr. of thiosinamin and $1\frac{1}{2}$ gr. of sodium salicylate.

Pharmacology

Externally.—Mustard is a powerful local **irritant, rubefacient** and **vesicant.** When it is first applied there is a sensation of warmth followed by severe burning pain, due to the irritant action of the mustard on the sensory nerves and increased local blood-supply. This irritation is quickly followed by paralysis, as a result of which there is loss of sensibility and a diminution both of the pain produced by the mustard and of any that may have existed previously. Mustard is also a **counter-irritant.** The excitation of the sensory nerves may reflexly stimulate the cardiac and respiratory centres.

Internally. **Gastro-intestinal tract.**—Taken in small doses as a *condiment*, mustard causes a sense of warmth in the stomach, stimulates the secretion of gastric juice and peristalsis, and therefore sharpens the appetite. In large doses, it acts as a prompt and efficient *emetic* without causing the usual depression.

Therapeutics

Externally.—A linseed poultice, having a little mustard (1 in 16) dusted over it, is a very common and efficacious **irritant** and **counter-irritant** in rheumatism, pleurisy, pneumonia, and bronchitis.

A mustard plaster will **soothe pain** in gastralgia, colic, neuralgia, lumbago, etc. When put over the epigastrium it often relieves vomiting, and when applied to the calves of the legs, it is a reflex stimulant in cases of syncope, asphyxia and coma.

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Severe headache, common colds, and febrile conditions specially in children, are greatly relieved by a hot pediluvium or foot-bath, whilst infantile convulsions may be checked by immersion of the whole of the patient's body in a mustard bath containing one tablespoonful of mustard to each gallon of water.

A mustard sitz bath, (*i.e.* hip bath) may be taken at the time of the period to induce menstruation when it has been suppressed by a chill.

Internally.—As an **emetic**, mustard is specially valuable in narcotic poisoning on account of its reflex stimulant effects. Give one to four teaspoonfuls in a tumbler of warm water.

Injections of thiosinamin soften the scar tissue and have been advocated for prolonged periods in *stricture of the œsophagus, stenosis of pylorus, perigastric adhesions, hour-glass contraction of the stomach, urethral stricture, middle ear deafness, Dupuytren's contraction*, etc., and in certain sclerotic spinal cord diseases. Some observers report no improvement as the result of numerous injections long continued, and the injections have, in some cases, been followed by the onset of purpura hæmorrhagica.

CAPSICUM

Capsicum

Syn.—Small Chillies; Guinea Pepper; Pod Pepper; Capsici Fructus.

Syn. I.V.—*Dhani Lanka*, Beng. *Gach Marich*, Hind.

Source.—The dried ripe fruit of *Capsicum minimum.*

Characters.—Dull orange-red, oblong, conical, obtuse, two-celled fruits: about 12 to 20 mm. long, up to 7 mm. wide; sometimes attached to a 5 toothed inferior calyx and a straight, slender pedicel. Pericarp somewhat shrivelled, glabrous, translucent, and leathery: containing 10 to 20 flat, reniform seeds, 3 to 4 mm. long. Odour, characteristic; taste, intensely pungent.

Composition.—(1) *Capsaicin* or *Capsacutin* (0.14 p.c.) a crystalline colourless pungent principle. (2) A liquid alkaloid. (3) An oleo-resin. (4) A fixed oil and red colouring matter.

B.P. Dose—½ to 2 grs. or 0·03 to 0·12 grm.

Official Preparations

1. **Tinctura Capsici.**—5 p.c. **B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**
2. **Unguentum Capsici.** *Syn.—Chillie Paste.*—25 p.c. approximately.

Pharmacology

Externally.—It is a powerful irritant, rubefacient and therefore counter-irritant.

Internally. **Alimentary canal.**—In small doses it stimulates the secretion of saliva and gastric juice and increases peristaltic movements. It is therefore a sialagogue, stomachic and carminative. In large doses it is a gastro-intestinal irritant.

It is a cardiac and vascular stimulant, feeble narcotic, diuretic and aphrodisiac.

Therapeutics

Externally.—Like cantharidin, capsicum may be used to promote the growth of hair. Emplastrum capsici (1 in 50 with resin plaster), or the ointment may be applied in rheumatism, lumbago or torticollis. A piece of lint soaked in an infusion of the pods and covered with oiled silk may be used for the same purpose.

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Internally.—It is chiefly used as a condiment in India. The tincture mixed with tannic acid (1 dr. of each in water 10 ozs.) makes a useful gargle in relaxed throat, simple tonsillitis and chronic pharyngitis. It is an excellent remedy in atonic and flatulent dyspepsia and dipsomania. In the last, it not only checks the craving but stimulates and tones the gastric functions. Tr. capsicum 2 drs., sp. ammon. arom. 6 drs., sodium bromide 2 drs., tr. cinch. co. 4 drs., aqua chlorof. to 8 ozs. $\frac{1}{12}$th part every 2 or 3 hours until the craving for drink is removed. The above prescription will generally be found to be an effective "pick me up."

CLASS D: Nauseants

ASAFOETIDA

Asafetida

Syn. I.V.—*Hing.*, Beng. *Hingra*, Hind., Bom.

Source.—An oleo-gum-resin obtained by incision from the living rhizome and root of *Ferula fœtida*, or other species of *Ferula*.

Characters.—In rounded or flattened masses, agglutinated; from 12 to 25 mm. in diameter, or dull yellow tears: darkening on keeping. Internally yellowish, translucent, or milky-white; opaque. Odour, strong, persistent alliaceous. Taste, bitter, acrid, alliaceous. When triturated with water froms a white emulsion.

Composition.—(1) *Volatile oil*, 6 to 17 p.c. containing essential oil of garlic, allyl persulphide which gives it its peculiar odour. (2) A resin, *asaresinotannol*, 65 p.c. (3) *Gum*, 25 p.c.

B.P. Dose.—5 to 15 grs. or 0·3 to 1 grm.

OFFICIAL PREPARATIONS

1. **Pilula Aloes et Asafœtidæ.**—30 p.c. **B.P. Dose.—4 to 8 grs. or 0·25 to 0·5 grm.**
2. **Tinctura Asafœtidæ.**—20 p.c. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

PHARMACOLOGY

Internally. **Gastro-intestinal canal.**—Like aromatic oils and resins, it is a stimulant, carminative and antispasmodic expelling flatus and relieving spasm; but its unpleasant nauseous taste is a drawback to its use.

Lungs.—It increases and disinfects bronchial secretion during its elimination. Hence it is a disinfectant expectorant.

Nervous system.—It reflexly stimulates the nervous system through the mouth and stomach.

Elimination.—By the bronchial secretion and urine.

THERAPEUTICS

Externally.—A thick emulsion prepared by triturating with water is often applied with benefit to the abdomen of infants in tympanites.

Internally.—It is rarely used now except as a sedative in hysteria and allied conditions and as a carminative in

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flatulence. In the latter condition it may be given as an enema (30 grs. rubbed up with water 4 ozs.). Cases of malingering may be cured sometimes by giving effervescing draughts containing a few minims of tinctures of asafetida and valerian, three or four times a day.

It is best given in pills, capsules or tincture.

VALERIANA

Valerian

Syn.—Valerianæ Rhizoma.

Source.—The dried rhizome and roots of *Valeriana officinalis*, collected in the autumn.

Characters.—*Rhizome:* 2 to 4 cm. long, entire or longitudinally divided; yellowish-brown externally, whitish internally; fracture, short, and horny; cortex parenchymatous with starch grains; endodermal cells contain volatile oil. *Roots:* Numerous, slender, brittle, 2 to 10 cm. long; piliferous layer papillose, with root hairs; exodermis of large cells containing volatile oil. Odour, strong and characteristic; taste, sweetish, camphoraceous and slightly bitter.

Composition.—Its chief constituent is a volatile oil, 1 p.c. consisting of *bornyl isovalerianate, formate, butyrate,* and *acetate,* united with *l-pinene, l-camphene,* and *l-limonene.* The oil has no odour when freshly distilled but on exposure to air develops the characteristic odour.

B.P. Dose.—5 to 15 grs. or **0.3 to 1 grm.**

Official Preparation

1. **Tinctura Valerianæ Ammoniata.—20 p.c. B.P. Dose.—30 to 60 ms.** or **2 to 4 mils.**

ZINCI VALERIANAS

Zinc Valerianate. (*Not official*)

Characters.—In white, pearly, tabular crystals with a characteristic disagreeable odour and metallic taste. *Soluble* in hot water and alcohol (90 p.c.).

Dose.—1 to 3 grs. or 0·06 to 0.2 grm.

Pharmacology and Therapeutics

Small doses of valerian, like other volatile oils, produce a sensation of warmth in the epigastrium, a quickened pulse, and some mental excitement. There are considerable differences of opinion as to the manner in which valerian produces its effects on the organism.

The ammoniated tincture is useful as a carminative in flatulence; and as a reflex stimulant in faintness and palpitation, but the essential oil (2 to 5 ms.) suspended in mucilage with cinnamon water is better.

It is largely used in hypochondriasis, hysteria, nervous headache and other neurotic conditions in the form of the tincture with bromides, or as an extract (1 to 5 grs.) with camphor monobromata for its supposed stimulating action on the psychical functions and the circulation. Its effects are however purely mental produced by its unpleasant taste and odour. In fact most of these cases yield to suggestion and use of charms, etc.

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CLASS E: **Carminatives and Flavouring Agents**

CARYOPHYLLUM

Clove

Syn. I.V.—*Lobanga*, Beng. *Long.* Hind.

Source.—The dried flower-buds of *Eugenia aromatica.*

Characters.—10 to 17.5 mm. long, bright reddish-brown wrinkled, sub-cylindrical: calyx, which tapers below is surrounded by four thick, rigid, patent teeth, between which are four paler imbricated petals enclosing stamens and a single style. Odour, strong fragrant, spicy. Taste, very pungent, aromatic.

Composition.—(1) *Volatile Oil* (*off.*) 15 to 20 p. c. (2) *Caryophyllin,* a crystalline body. (3) *Gallo-tannic acid.* (4) resin, etc.

B.P. Dose.—2 to 5 grs. or **0.12 to 0.3 grm.**

Enters into.—Pulv. Cretæ Arom.

OFFICIAL PREPARATIONS

1. **Infusum Caryophylli Concentratum.—B.P. Dose.—30 to 60 ms.** or **2 to 4 mils.**
2. **Infusum Caryophylli Recens.**—2·5 p.c. Should be used within twelve hours of its preparation. **B.P. Dose.—½ to 1 oz.** or **15 to 30 mils.**

OLEUM CARYOPHYLLI

Oil of Clove

Source.—The oil distilled from Clove. Contains between 85 to 90 p.c. v/v of *eugenol*, $C_{10}H_{12}O_2$.

Characters.—Colourless or pale yellow liquid when recent, becoming reddish-brown gradually. Sp. gr. 1.047 to 1.060. Heavier than water.

Composition.—(1) *Eugenol*, chemically resembling phenol. (2) *Aceteugenol.* (3) *Caryophyllene*, a sesquiterpene, furfural and methyl-amyl-ketone.

B. P. Dose.—1 to 3 ms. or **0.06 to 0.2 mil.**

PHARMACOLOGY

Externally.—Oil of clove acts like camphor, and is therefore a local stimulant, rubefacient, counter-irritant and anæsthetic. It is also a parasiticide and antiseptic.

Internally. **Mouth.**—The local action of the oil of clove on the mouth is the same as on the skin. It reflexly stimulates the secretion of saliva and mucus and sharpens the appetite by stimulating the nerves of taste and smell. Simultaneously, the gastric circulation is reflexly excited with increased flow of the gastric juice.

Stomach.—On reaching the stomach it directly stimulates the stomach, thereby increasing the secretion of the gastric juice and stimulating the peristaltic movements. It is therefore a stomachic tonic and carminative. Like camphor or alcohol, it also reflexly stimulates the heart and moderately increases the rate and force of the pulse.

Intestine.—Some of the oil finding its way into the bowels produces the same action there as on the stomach, causing increased secretion, increased peristalsis and increased expulsion of flatus, but no absorption of gases, relieving any spasm, if present. Hence it is an intestinal antispasmodic.

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Heart, blood and circulation.—It enters the blood unchanged and is partly oxidised by the red blood-corpuscles. It increases the number of white corpuscles. The heart may be stimulated to a slight extent by its direct action on it, but chiefly by the reflex action from the stomach. By temporarily exciting the cerebral, medullary and spinal centres either directly through the circulation, or, as is generally the case, reflexly from the stomach, it increases the functional activity of the organs and relieves spasmodic contractions of the various parts of the body.

Elimination.—Like other volatile oils it is eliminated by the kidneys, genito-urinary tract, skin, bronchial mucous membrane, liver, and probably the bowels. In its passage it stimulates and disinfects their secretions but not so powerfully as turpentine or many other volatile oils.

Therapeutics

Externally.—On account of its high price oil of clove cannot be freely used. Occasionally it is applied as an *anodyne* in superficial neuralgias. Very often it is employed for flavouring hair-oils and liniments. It is also very useful for *keeping off mosquitoes* for which purpose a little should be rubbed on to the hands and feet immediately before retiring to rest. In this way it acts as a prophylactic against malaria.

Internally.—Clove is generally used in cookery to improve flavour, and with aromatic bitters, to stimulate appetite and digestion. The oil relieves toothache when put into the cavity of the decayed tooth. It is an excellent remedy for intestinal colic and flatulence. It may be combined with purgatives to prevent their griping.

Prescribing hints.—The oil is best given on a lump of sugar or triturated with sugar as *elæosacchara*, or suspended in mucilage.

CARDAMOMUM

Cardamom

Syn.—Cardamomi Semina. **Syn. I.V.**—*Elachi*, Beng.

Source.—The dried ripe or nearly ripe seeds of *Elettaria Cardamomum*. The seeds should be kept in their pericarps and separated when required for use.

Composition.—(1) A *volatile oil*. (2) A fixed oil. The pericarp is inactive medicinally.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm.

Official Preparation

1. **Tinctura Cardamomi Composita.—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Pharmacology and Therapeutics

Internally.—Cardamom seeds are stimulant, stomachic and carminative and are therefore useful in flatulence and for correcting the griping property of purgatives. The tincture is a colouring and flavouring agent.

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CARUM

Caraway

Syn.—Caraway Fructus. **Syn. I.V.**—*Jira*, Hind.
Source.—The dried fruit of *Carum Carvi*.
Characters.—Mericarps separate; each 7 mm. long, 2 mm. broad; brown, with paler ridges; slightly curved, tapering, glabrous. Odour, aromatic. Taste, aromatic, agreeable.
Composition.—(1) The *volatile oil* (*off.*).
B.P. Dose.—10 to 30 grs. or **0.6 to 2 grm.**

OLEUM CARI

Oil of Caraway

Source.—The oil distilled from Caraway and rectified. Contains 53 to 63 p.c. w/w of *carvone*, $C_{10}H_{14}O$.
Characters.—Colourless or pale yellow, having the odour and taste of the fruit. Sp. gr. 0.910 to 0.920.
Composition.—(1) *Carvone* an unsaturated ketone. (2) Terpene or *d*-limonene, also called *Carvene*. (3) *Cymene*.
B.P. Dose.—1 to 3 ms. or **0.06 to 0.2 mil.**

USES :—The same as those of anethi fructus.

CORIANDRUM

Coriander

Syn.—Coriandri Fructus. **Syn. I.V.**—*Dhania*, Beng., Hind.
Source.—The dried ripe fruit of *Coriandrum sativum*.
Characters.—Nearly globular, 3 mm. in diameter, uniform, brownish-yellow, glabrous. Two mericarps closely united, and crowned by calyx teeth and stylopod. Odour, aromatic, especially when *bruised*. Taste, agreeable.
Composition.—*The Volatile Oil* (*off.*).
B.P. Dose.—5 to 15 grs. or **0.3 to 1 grm.**

OLEUM CORIANDRI

Oil of Coriander

Source and characters.—A colourless or pale-yellow oil obtained by distilling Coriander. *Solubility.*—1 in 3 of alcohol (90 p.c.). Sp. gr. 0.870 to 0.884.
Composition.—(1) *Coriandrol*, the dextro-isomeride of linanol. (2) *d-pinene*, *l-pinene*, geraniol and borneol.
B.P. Dose.—1 to 3 ms. or **0.06 to 0.2 mil.**

PHARMACOLOGY AND THERAPEUTICS

The action and uses of coriander fruit resemble more or less those of dill and anise fruits. The oil is specially used to render medicines more palatable and to prevent griping. The fruit is used in Indian cookery, and its mericarps are chewed with prepared *pan* or sometimes alone to remove the after-taste of drugs.

ANETHUM

Dill

Syn.—Anethi Fructus. **Syn. I.V.**—*Soya*. Hind.
Source.—The dried ripe fruit *Anethum graveolens*.
Characters.—The fruit consists of two mericarps freed from pedicel. Each is broadly oval; 4 mm. long, 2 to 3 mm. broad; compressed dorsally; brown,

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dorsal ridges inconspicuous, but lateral ones prolonged into *wings*. Each mericarp exhibits 6 vittæ. Odour and taste, aromatic.

Composition.—The *volatile oil*.

Official Preparation

1. **Aqua Anethi Destillata.**—1 in 20. **B.P. Dose.**—½ to 1 oz. or 15 to 30 mils.

OLEUM ANETHI

Oil of Dill

Source.—Obtained by distilling Dill. Contains 44 to 63 p.c. w/w of *carvone*, $C_{10}H_{14}O$.

Characters.—Colour, pale yellow; odour, that of the fruit; taste, sweet, aromatic. Sp. gr. 0.900 to 0.915. *Solubility.*—In alcohol and ether.

Composition.—(1) A *Terpene* (*d-limonene*). *Carvone*.

B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

Official Preparation

1. **Aqua Anethi Concentrata.**—0.2 p.c. **B.P. Dose.**—5 to 15 ms. or 0.3 to 1 mil.

Pharmacology and Therapeutics

Dill and oil of dill are aromatics, stimulants, antiseptics, and carminatives and are used to relieve flatulency and intestinal colic. The oil corrects the griping of purgatives. Dill water is chiefly used to remove flatulence in children.

OLEUM ANISI

Oil of Anise

Source.—Obtained by distilling dried ripe fruits of *Pimpinella Anisum* or star-anise fruit, *Illicium verum*.

Characters.—Colourless, or pale yellow, liquid; odour of the fruit; taste, mildly aromatic. Sp. gr. 0.980 to 0.994.

Composition.—(1) *Anethole* 80 to 90 p.c. (2) *Anisic aldehyde*. (3) *Methyl chavicol*.

B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

Pharmacology and Therapeutics

The action and uses of anise are almost identical with those of dill, except that it has a slight expectorant property and is often prescribed as a vehicle for cough mixtures.

LIMONIS CORTEX

Lemon Peel

Source.—The fresh outer part of the pericarp of the fruit of *Citrus Limonia*.

Characters.—Outer surface, pale yellow, more or less rough; with a small amount of white spongy part of pericarp on the inner surface: numerous large oil glands and crystals of calcium oxalate below the epidermis. Odour, characteristic, fragrant. Taste, aromatic, bitter.

Composition.—(1) *Volatile oil, oleum limonis* (*off.*). (2) *Hesperidin*, a bitter principle.

Official Preparations

1. **Oleum Limonis.**—Oil expressed from *Lemon Peel*. A pale yellow, or greenish-yellow liquid; odour, that of lemons; taste, warm, slightly bitter. *Sp. gr.* 0.857 to 0.861. Contains not less than 4 p.c. w/w of aldehydes, calculated as *citral*, $C_{10}H_{16}O$. **B.P. Dose.**—1 to 3 ms. or 0.06 to 0.2 mil.
2. **Syrupus Limonis.**—Peel 6 p.c. **B.P. Dose.**—30 to 120 ms. or 2 to 8 mils.
3. **Tinctura Limonis.**—Peel 25 p.c. **B.P. Dose.**—30 to 60 ms. or 2 to 4 mils.

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Pharmacology and Therapeutics

Internally.—The action of lemon peel is similar to that of orange peel. The oil is a stimulant and carminative and can be used to expel intestinal flatus. In practice both of them are used for flavouring purpose. Lemon juice is antiscorbutic and contains vitamin C.

FOENICULUM

Fennel

Syn. I.V.—*Bari Sanf, Saurif,* Hind.
Source.—The dried ripe fruit of *Fœniculum vulgare.*
Characters.—Mericarps up to 10 mm. long, 4 mm. broad; small, oblong, curved, glabrous; greenish-brown or pale-yellowish brown. Odour, aromatic. Taste, aromatic, sweet. The fruit is readily separated into 2 mericarps each of which has 5 prominent primary ridges, and exhibits in transverse section 6 large vittæ.
Composition.—(1) A *Volatile oil,* 3 to 4 p.c. which contains *anethole* and *fenchone.*
Enters into.—Pulv. Glycyrrhizæ Co.
B.P. Dose.—**5 to 10 grs.** or **0.3 to 0.6 grm.**

Uses.—The same as those of oil of anise or of dill.

CINNAMOMUM

Cinnamon

Syn. I.V.—*Dalchini.* Beng. and Hind. *Gudatvak,* Sans.
Source.—The dried inner bark of the shoots of coppiced trees of *Cinnamomum zeylanicum.*
Characters.—In rolled quills; thin, brittle, splintery, light yellowish-brown; 9 mm. in diameter. Odour, fragrant. Taste, warm, sweet and aromatic.
Composition.—(1) *Volatile oil (off.).* (2) *Tannin.* (3) *Sugar.* (4) *Gum.*
B. P. Dose.—**5 to 20 grs.** or **0.3 to 1.2 grm.**
Enters into.—Pulv. Cretæ Arom., Tr. Card. Co.

Official Preparation

1. **Aqua Cinnamomi Destillata.**—1 in 10. **B. P. Dose.**—½ **to 1 oz.** or **15 to 30 mils.**

OLEUM CINNAMOMI

Oil of Cinnamon

Syn.—Oleum Cassiæ, U.S.P.
Source.—The oil distilled from Cinnamon Bark.
Characters.—Yellowish when fresh, becoming reddish brown with age. Sp. gr. 1.000 to 1.030. *Sinks in water.*
Composition.—(1) *Cinnamic aldehyde,* 58 p.c. (2) *Cinnamic acid.* (3) *Eugenol.*
B. P. Dose.—**1 to 3 ms.** or **0.06 to 0.2 mil.**

Official Perparation

1. **Aqua Cinnamomi Concentrata.**—**B. P. Dose.**—**5 to 15 ms.** or **0.2 to 1 mil.**

Pharmacology and Therapeutics

Internally.—The action and uses of cinnamon bark and its oil resemble those of cloves and the oil of cloves but the bark has besides a mild astringent property. As a flavouring and

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correcting agent both the bark and the oil are used. The writer has found the bark useful in mucous diarrhœa. The oil is used in combination with other drugs as an intestinal antiseptic in typhoid fever. It is perhaps useful in preventing tympanitic distension.

MYRISTICA

Nutmeg

Syn. I.V.—*Jaiphal*, Beng., Hind.

Source.—The dried kernel of the seeds of *Myristica fragrans.*

Characters.—Broadly oval or rounded, about 20 to 30 mm. long. Externally, greyish-brown, with reticulated furrows. Internally, greyish-red marbled with brownish-red veins. Odour, strong, aromatic. Taste, aromatic, warm, bitter.

Composition.—(1) A *fixed oil* consisting of glyceryl oleate, glyceryl butyrate, and glyceryl myristate, 25 to 30 p.c. (2) *Amylodextrin.* (3) *Volatile oil*, (5 to 15 p.c.).

Enters into.—Pulv. Cretæ Aromat.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

OLEUM MYRISTICAE

Oil of Nutmeg

Source and characters.—A pale yellow oil, distilled from Nutmeg, having the odour and taste of nutmeg. *Solubility.*—1 in 3 of alcohol (90 p.c.). Sp. gr. 0.880 to 0.925.

Composition.—(1) *Myristicin*, a terpene. (3) A terpene, *d-camphene.*

B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

Enters into.—Spt. Ammon. Aromat., Tr. Valerian. Ammon.

Pharmacology and Therapeutics

Externally.—The volatile and the fixed oils are used for perfuming pomades and lotions for the hair, and diluted with olive oil or soap-liniment as an embrocation in chronic rheumatism. The expressed oil is said to possess antiseptic and antiparasitic properties. Nutmeg made into a paste is sometimes used by the people of India to remove headaches and neuralgia.

Internally.—For its agreeable aroma it is used in cooking. Both the kernel and the volatile oil are gastric stimulants, increasing the flow of gastric juice, and carminatives, expelling intestinal flatus; hence they can be used in dyspepsia, cramps and flatulence. The volatile oil relieves toothache, and the kernel is chewed to remove fœtor of breath. In large doses it acts as a powerful narcotic, causing giddiness, vertigo and coma, symptoms resembling those that follow poisonous doses of camphor.

OLEUM LAVANDULAE

Oil of Lavender

Source.—The oil distilled from the fresh flowering tops of *Lavandula officinalis.* Contains 7 to 14 p.c. w/w of linalyl acetate, $C_{12}H_{20}O_2$.

Characters.—Pale yellow or yellowish-green with fragrant odour of the flowers and a pungent bitter taste. Sp. gr. 0.882 to 0.900. *Solubility.*—1 in 4 of alcohol (70 p.c).

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Composition.—(1) *Linalol*, an alcohol, and its acetic ester, *linalyl acetate*, are the principal constituents. (2) Pinene, $C_{10}H_{16}$, is present in some samples but is not a constant constituent. (3) Limonene geraniol and a sesquiterpene.

B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

Non-official Preparation

1. **Tinctura Lavandulæ Co.**—Oils of lavender and rose, cinnamon bark, nutmeg, red sanders wood and alcohol (90 p.c). *Dose.*—30 to 60 ms. or 2 to 4 mils.

Pharmacology and Therapeutics

Externally.—Oil of lavender is used to perfume liniments, and the tincture to colour lotions. It is an ingredient of smelling salts and lavender water.

Internally.—Like other aromatic oils, it is a stimulant, carminative and antispasmodic, and can be used in flatulence, colic, hypochondriasis, hysteria and neurasthenic affections. But the chief use of the tincture is confined to colouring and flavouring purposes.

OLEUM MENTHAE PIPERITAE

Oil of Peppermint

Source.—The oil distilled from fresh flowering tops, *Mentha piperita*, and rectified, if necessary. Contains 4.5 to 9 p.c. w/w *menthyl acetate*, and 46 p.c. w/w free *menthol*.

Characters.—Colourless, pale-yellow or greenish-yellow when fresh, becoming darker by age. Odour of the herb. Taste, aromatic, followed by a sensation of of coldness. Sp. gr. 0.902 to 0.910. *Solubility.*—1 in 4 of alcohol (70 p.c.).

B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

Enters into.—Pil. Rhei Co.

Official Preparations

1. **Aqua Menthæ Piperitæ Concentrata.**—1 in 50. **B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**
2. **Aqua Menthæ Piperitæ Destillata.**—1 in 1000. **B.P. Dose.—½ to 1 oz. or 15 to 30 mils.**
3. **Spiritus Menthæ Piperitæ.**—1 in 10. **B.P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

Pharmacology and Therapeutics

Externally.—The action of the oil of peppermint resembles that of the volatile oils generally. But owing to the presence of menthol, the sensation of coldness and numbness after a feeling of warmth is more marked. Hence, it is a local anæsthetic, and is therefore used to allay the pain of superficial neuralgias and herpes zoster. It is also a powerful antiseptic. It relieves toothache due to a carious tooth. The smell of the oil keeps off mosquitoes.

Internally.—For its powerful antispasmodic and carminative properties, it is often used to relieve flatulent colic and spasmodic pains of the stomach. It corrects the griping effect of purgatives and covers the nauseous taste of drugs.

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ZINGIBER

Ginger

Source.—The scraped and dried rhizome of *Zingiber officinale.*

Characters.—Flattish, irregularly branched pieces, about 7 to 15 cm. long, 1.5 to 6.5 cm. wide; 1 to 1.5 cm. thick; each branch crowned by a depressed scar. Externally pale buff, striated fibrous. Fracture, short, rather fibrous. Odour, well known, agreeable, and aromatic. Taste, strong, pungent.

Composition.—(1) An aromatic volatile oil, 1 to 3 p.c. (2) *Gingerol*, a yellowish oily body to which pungency is due. (3) Resin and starch.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Enters into.—Infusum Sennæ Rec., Pulv. Jalapæ Co., Pulv. Rhei Co.

Official Preparations

1. **Tinctura Zingiberis Fortis.** *Syn.—Essence of Ginger.* **B.P. Dose.—5 to 10 ms. or 0.3 to 0.6 mil.**
2. **Tinctura Zingiberis Mitis.—1** in 5 of strong tincture. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**
3. **Syrupus Zingiberis.—B.P. Dose.—30 to 120 ms. or 2 to 8 mils.**

Pharmacology and Therapeutics

Ginger is a powerful aromatic stimulant, acting like capsicum and cardamoms. Chewed, it is a valuable sialagogue; and used as snuff, it is a powerful errhine, but it is chiefly given as a stomachic, carminative and flavouring agent. Commercial gingerin, which is an oleo-resin, is a useful addition to purgative pills to prevent griping. The dose is $\frac{1}{4}$ to 3 grains.

GROUP XVIII

SOLID VOLATILE OILS (Stearoptenes)

Camphor, Menthol, Thymol

CAMPHORA

Camphor. $C_{10}H_{16}O$

Syn. I.V.—*Karpur*, Beng. *Kafur, Kapur*, Hind

Source.—Obtained from *Cinnamomum Camphora*, and purified by sublimation.

Characters.—Colourless, transparent, crystals or crystalline masses, of tough consistence; also in rectangular tablets or pulverulent masses—"Flowers of Camphor." Sp. gr. 0.995. Odour penetrating. Taste, bitter, pungent, followed by a sensation of cold. Burns and volatilises. *Solubility.*—1 in 700 of water, 1 in 1 of alcohol (90 p.c.), in 0·25 of chloroform, very soluble in ether. It forms a liquid when triturated with chloral hydrate, menthol, phenol, or thymol.

B.P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.; 1 to 3 grs. or 0.06 to 0.2 grm. (subcutaneous).

Enters into.—Lint. Terebinthinæ.

Official Preparations

1. **Aqua Camphoræ.—1** in 1000 w/v. **B.P. Dose.—½ to 1 oz. or 15 to 30 mils.**
2. **Linimentum Camphoræ.** *Syn.—Camphorated Oil.*—20 p.c. w/w of camphor.

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3. **Linimentum Camphoræ Ammoniatum.** *Syn.—Lint. Camphor. Co.*—12·5 p.c. camphor.

4. **Linimentum Terebinthinæ Aceticum.**—Prepared with camphor liniment.

5. **Spiritus Camphoræ.** *Syn.—Tr. Camphoræ.*—10 p.c. **B.P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

6. **Tinctura Opii Camphorata.** *Syn.—Tr. Camphor Co.; Paregoric.* —$\frac{1}{3\frac{1}{7}}$ gr. morphine in 60 ms. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Non-official Preparations and Derivatives

1. **Acidum Camphoricum.**—A white, crystalline powder, slightly soluble in water. In *phthisical night-sweats* and *vesical catarrh. Dose.*—8 to 30 grs. or 0·5 to 2 grm.

2. **Injectio Camphoræ Hypodermica.**—Camphor 1, sterile olive oil to 5. *Dose.*—10 to 30 ms. or 0.6 to 2 mils.

3. **Camphora Monobromata.**—In colourless prisms, insoluble in water. A hypnotic and nervous sedative in *hysteria, chorea, delirium tremens,* and *petit mal,* also used in *spermatorrhœa. Dose.*—2 to 8 grs. or 0·12 to 0·5 grm.

4. **Cardiazol.**—*Pentamethylenetetrazol.*—A water soluble complex preparation with action similar to camphor but superior in all cases of severe circulatory disturbance. May be used by mouth, subcutaneously or intravenously as an analeptic of rapid and reliable action of satisfactory duration. It stimulates the respiratory centre. Valuable in *collapse of angina, myocarditis* and *circulatory insufficiency. Dose.*—1 c.c. subcutaneously, or 0.1 grm. *per os* in tablets.

5. **Carditone.**—Sodium campho-sulphonate 15 p.c. in aqueous solution. A general cardiac stimulant, also increases respiratory rate and volume. In shock, heart failure, coma, poisoning by coal gas and narcotics. *Dose.—Subcutaneously,* 1 to 2 c.c.; *intravenously* up to 2 c.c.: by *mouth,* 25 to 100 ms. (1.5 to 6 mils) per day diluted with water. This solution should not be used parenterally.

6. **Coramine.**—*Pyridine-β- carboxylic acid diethylamide.* A yellowish liquid, almost colourless and tasteless. Miscible with water in all proportions. *Dose.*—1 to 2 mils of the 25 p.c. solution, by *mouth* or by *subcutaneous, intramuscular* or *intravenous injection.* Valuable *cardiac* and *respiratory stimulant,* action being on the vital centres in the medulla. Specially valuable in failure of heart and respiration after excessive doses of narcotics and in bad cases of barbiturate poisoning.

Pharmacology

Externally.—Camphor being a stearoptene, acts like volatile oils. It is moderately **antiseptic,** though weaker than many volatile oils, *e.g.*, the coal-tar series or the phenol group of drugs. It stimulates the local vessels and causes redness and heat, thus acting as a rubefacient. It first stimulates, then depresses the local nerves producing a sensation of coolness, although the vessels are dilated.

Internally. **Alimentary tract.**—It has a peculiar bitter taste and produces a sensation of coldness soon followed by that of warmth in the mouth. It stimulates the local circulation and the secretion of saliva and mucus in the mouth. In the stomach it (1) causes a sense of warmth, (2) dilates the blood-vessels, (3) increases the flow of gastric juice, and (4) stimulates the peristaltic movements and relaxation of the sphincters. It is therefore a gastric stimulant and carminative, but in large doses it irritates the stomach and causes nausea and vomiting. It is also an antiseptic to the intestine and relieves spasm.

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Heart and circulation.—The knowledge of the action of camphor on the heart and circulation is incomplete and uncertain, although clinical experience indicates that it is a circulatory stimulant. Injected directly into the circulation it increases the arterial pressure, but this effect is not constant or persistent and often it produces no rise at all. In some experiments it has been observed to stimulate the heart, while others did not observe any change. It probably stimulates the cardiac muscle. The coronary vessels are dilated but it is not certain whether this occurs in therapeutic doses (Cushny). It has been suggested that although camphor has no action on the normal heart, it improves the heart which is depressed or irregular. It dilates the vessels of the skin and gives a sensation of warmth like alcohol. It is possible that by dilating the vessels of the skin and the coronary arteries it effects a re-distribution of the blood much in the same way as strychnine (*see* page 209). Being an irritant when given as an injection, it provokes reflex medullary stimulation (Gunn).

Respiration.—It slightly stimulates the bronchial secretion by increasing the vascularity of the bronchial mucous membrane and acts as a feeble **expectorant.** The respiratory movements are hardly affected although it may be accelerated during convulsion.

Nervous system.—It stimulates the cerebrum and in large doses produces excitement, giddiness, confusion of ideas, inco-ordination of movement and sometimes convulsion. Loss of consciousness and stupor may appear later. With some it acts as an **exhilarant,** causing agreeable hallucinations with a desire to laugh or dance, and with others no excitement is observed, the effect being one of depression with drowsiness and **stupor.** It first stimulates and then depresses the reflex movements and acts as an antispasmodic. The respiratory and vaso-motor centres are stimulated.

Skin.—Some dilatation of the skin vessels follows the use of camphor by the mouth, due possibly to gastric irritation. It is excreted with the sweat, which it increases by directly affecting the sweat-centres and locally the sweat-glands.

Temperature.—It has very little effect on temperature in health, but is a mild **antipyretic** in fever, due chiefly to loss of heat from dilatation of the skin vessels.

Genital organs.—In moderate doses it is said to act as an aphrodisiac and in large doses as an anaphrodisiac.

Elimination.—Camphor is partially oxidised in the tissues forming camphorol which combines with glycuronic acid and is excreted by the kidneys.

Acute toxic action.—Poisoning by camphor is rare. The writer has seen only one case of poisoning. Epigastric pain, nausea, sometimes vomiting, giddiness, dimness of sight, delirium verging on mania,

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epileptiform convulsions, cyanosis, paralysis, cold clammy perspiration, strangury or arrest of urinary secretion, coma and death.

Antidotes.—Emetics, pump, brisk saline cathartics, cold and hot douches, counter-irritation, sometimes stimulants, and strychnine hypodermically if necessary.

Chronic toxic action.—Young women sometimes make a habit of taking camphor regularly with a view to improve their complexion. This habit if once contracted is very difficult to shake off. Mild form of exhilaration, stupefaction, extreme weakness, and pallor are the chief symptoms.

THERAPEUTICS

Externally.—Camphor is a favourite ingredient of many liniments, for lessening the pain of fibrositis, myalgia and chronic rheumatism. The ammoniated camphor liniment and the turpentine and acetic acid liniment are very effective counter-irritants in bronchitis, pleuritis and broncho-pneumonia. Camphor has been used in combination with dusting powders on eczema and intertrigo. Mixed with zinc ointment (½ dr. to 1 oz.) it allays the itching of eczema genitalis. Chloral-camphor and menthol camphor are most valuable local anodynes in superficial neuralgias.

Internally. **Alimentary canal.**—Mixed with chalk it is used as tooth-powder (1 in 8). Chloral-camphor relieves toothache when put into a carious tooth. Camphor water is a domestic carminative for flatulence and colic of children. Spirit of camphor may be given in flatulence and colic of adults. Very few drugs can excel camphor in summer diarrhœa and cholera. It should be given in these cases from the commencement of the illness in 5 to 6 ms. doses of the spirit every 10 or 15 minutes till the symptoms abate, and then hourly. It is useless in the later stages.

Respiratory tract.—The inhalation of camphor or its use in the form of snuff relieves coryza and that form of chronic catarrh which is characterised by paroxysmal sneezing. At the same time 5 drops of the spirit should be given by the mouth every 15 minutes. It is especially useful in chronic bronchitis if given either in the form of paregoric or in the form of a pill in combination with hyoscyamus.

Circulation.—Camphor is absorbed very slowly from the alimentary tract, it should therefore be used hypodermically as a circulatory stimulant. It is used to stimulate the heart in the later stages of infectious fevers, pneumonia, septicæmia, etc. Dissolved in oil or ether (1 to 2 grs. in 1 c.c.) it is valuable in threatened failure of the heart and respiration. But many doubt its efficacy.

Nervous system.—In many spasmodic affections, such as nervous palpitation, chorea, hysteria, etc., it has been given with doubtful results.

Genital organs.—Large doses check inordinate sexual desire and chordee. Applied to the breast and given by the mouth in 3 gr. doses camphor acts as an antigalactagogue.

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Prescribing hints.—It is best given dissolved in milk (1 dr. in 1 oz.), which also covers its unpleasant taste. The spirit may be taken on sugar, or in emulsion. Powdered camphor may be given in pills or cachets. Hypodermically it may be given dissolved in olive oil (1 in 5) or ether.

MENTHOL

Menthol. $C_{10}H_{20}O$

Source.—A saturated cyclic alcohol, *p*-menthan-3-ol, obtained from the volatile oils of various species of *mentha*.

Characters.—Colourless, acicular or prismatic crystals; Odour, penetrating, resembling that of peppermint; taste, warm and aromatic, followed by a sensation of cold. *Solubility.*—Very slightly in water, readily in alcohol (90 p.c.).

B. P. Dose.—½ to 2 grs. or 0.03 to 0.12 grm.

Non-official Preparations

1. **Spiritus Mentholis Compositus, B.P.C.**—Camphor, menthol, each 2 oz., terebene, eucalyptol, each 2 oz., alcohol (90 p.c.), *q.s.* 20 oz. *Dose.*—10 drops by inhalation.
2. **Menthyl Valerianate.** *Syn.*—*Validol.*—A solution containing 30 p.c. of menthol valerianate. A colourless liquid with an agreeable smell and no burning taste. Nervous sedative; used in *sea sickness, hysteria* and *neurasthenia. Dose.*—10 to 15 ms. either in wine or on a lump of sugar.
3. **Insufflatio Mentholis et Cocainæ, B.P.C.**—Menthol 2.5, Cocaine Hydrochloride 0.14, Ammonium Chloride 25.0, Camphor 5, Lycopodium to 100. In *coryza* as a snuff.
4. **Nebula Cocainæ Co., B.P.C.**—Cocaine 5 gm., Nebula Mentholis et Thymolis Co. to 1000. In *bronchitis, laryngitis* and *asthma* as a spray.
5. **Nebula Mentholis et Thymolis Co., B.P.C.**—Menthol, camphor and phenol each 2, thymol 0·2, liquid paraffin to 100.

Pharmacology and Therapeutics

Externally.—Locally applied menthol causes first stimulation, soon followed by a feeling of coldness, numbness and anæsthesia of the part, and thereby relieves the pain of neuralgias and other superficial pains. This is done by either drawing over the skin solid menthol, or by painting it with linimentum menthol, or a liquefied preparation, such as menthol cum camphor, menthol cum chloral, or by plaster. Any painting near the eyes causes a free flow of tears from the vapour. The plaster or liniment is often found useful in rheumatic and pleurodynic pains, lumbago and sciatica. Mentholeate, (menthol and oleic acid equal quantity), alcoholic solution (1 in 8), or menthol ointment (5 to 30 grs. in 1 oz. of vaseline or simple ointment), relieves pruritus. The ointment is specially useful in pruritus pudendi et ani.

Menthol when rubbed up with either thymol, phenol, chloral hydrate, camphor or butyl chloral, forms an oily liquid, which is an excellent remedy for toothache. It should be put into the cavity of the carious tooth and covered with a pledget of absorbent cotton.

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Menthol is also a powerful **antiseptic** and **antiparasitic**, its alcoholic solution or liniment has given good results in ringworm of the scalp. As a snuff (menthol 5 grs. in 1 oz. of starch, talc or oxychloride of bismuth, or along with boric acid 2, and ammon. chloride 3 parts) it is efficacious in influenza, hay fever, catarrh and ozæna.

Internally.—The alcoholic solution has been painted in diphtheria. The pigment (1 to 4 of olive oil, 20 to 30 ms.) has been injected into the larynx for laryngeal and tracheal tubercle and bronchiectasis with good effects. The anæsthetic effect lasts about 24 hours after a few injections. Menthol 1 gr. in olive oil 1 oz. has been usefully injected for thread-worms. It is rarely used internally, except as a corrigens of griping purgative pills, and in ½ to 1 gr. doses with extract of belladonna in flatulence and intestinal colic.

Menthol enters into the composition of many prescriptions used in the continuous inhalation treatment of pulmonary tuberculosis.

THYMOL

Thymol. $C_{10}H_{14}O$

Source.—A crystalline phenol obtained from the volatile oils of *Thymus vulgaris*, of *Monarda punctata*, and of *Trachyspermum Ammi*, or prepared synthetically.

Characters.—Colourless crystals; odour, pungent, aromatic and thyme-like; taste, pungent and aromatic. Sinks in cold water. *Soluble* in 1000 parts of water, in 1 part of alcohol (90 p.c).

B.P. Dose.—½ **to 2 grs. or 0.03 to 0.12 grm; 15 to 30 grs. or 1 to 2 grms.** *as anthelmintic.*

Non-official Preparations

1. **Volckmann's Thymol Solution.**—Thymol 0.1, alcohol 2, glycerin 2, dissolve and add water to 100. As a *spray* and *antiseptic lotion.*

2. **Unguentum Thymol.**—In varying strengths from 5 to 30 grs. in 1 oz of vaseline. The thymol must be dissolved in the basis by the aid of heat.

3. **Thymol Carbonate.** *Syn.—Thymotal.*—A nearly tasteless, colourless crystalline powder. Is not dissolved in the stomach and therefore valuable as a remedy for *Ankylostomum duodenale. Dose.*—5 to 15 grs. or 0.3 to 1 grm.

4. **Liquor Thymolis Co., B.P.C.** *Syn.—Liquor Antisepticus.*—Boric acid 29.03, benzoic acid 1.14, thymol 0.57, eucalyptol 1.25, menthol 0.38, oil of peppermint 0.31, oil of gaultheria 0.31, oil of thyme 0.31, tr. baptisia 50, alcohol 250·0, water to 1000. Used internally as a mild antiseptic in flatulence, and diarrhœa. Diluted used as an antiseptic mouth wash. Resembles proprietary preparation **Listerine.** *Dose.*—5 to 30 ms. or 0.3 to 2 mils.

Pharmacology and Therapeutics

Thymol is a very powerful antiseptic. A solution of the strength of 1 in 1000 stops all putrefactive or fermentative action in any fluid to which it is added. It is therefore more powerful than phenol; it is also less apt to cause eczema but its insolubility is a great draw-back. Volckmann's solution, the gauze and the ointment are all employed in *antiseptic surgery* and the last mentioned is very useful in parasitic

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skin diseases, especially tinea of the scalp or beard. Burns washed first with a watery solution (½ gr. in 1 oz.) and then treated with an oleaginous solution (½ gr. in 1 dr.) heal rapidly. The pastils, spray and inhalation are useful in laryngitis and pharyngitis.

Internally.—In large doses, thymol gives rise to very unpleasant symptoms, excitement, vertigo, etc., and the urine may become green. In still larger doses the medullary and spinal centres are paralysed, collapse sets in, and there is a marked fall of blood-pressure and temperature before death.

Its chief value, however, is as an **anthelmintic** for ankylostomum duodenale, for which purpose it must be given in doses of 15 to 30 grs., repeated 3 or 4 times at intervals of an hour; 60 grs. should be the maximum dose for a healthy adult, but usually 45 grs. would suffice. Such large doses however may cause abortion in women, therefore when treating pregnant women the dose should not be more than 30 grs. given in three doses of 10 grs. each. For weak, anæmic, and those with bad heart the dose should be less.

Prescribing hints.—Thymol *should not be administered in solution*, as it causes a most unpleasant burning sensation of the mouth and throat and is extremely irritating to the mucous membrane of the stomach. It should be given in pill, cachet, or emulsion. The emulsion is best made by dissolving the thymol in alcohol, and then precipitating it by pouring the alcoholic solution into cold water. A little mucilage may finally be added to keep the finely powdered thymol in suspension. The patient must keep to his bed and lie down for several hours after the last dose; he must also be warned not to partake of alcohol or any other solvent of thymol as long as the drug is in his stomach, otherwise serious consequences may ensue. It is not a suitable drug for the old or for children. It should be followed by a saline purge, and castor oil should not be used.

GROUP XIX

ANTISEPTICS, DISINFECTANTS AND PARASITICIDES

Antiseptics are substances which prevent or retard the growth of micro-organisms as long as they remain in contact with them but do not destroy them.

Disinfectants destroy pathogenic microbes, *i.e.*, those which cause communicable diseases; *deodorants* destroy offensive or disagreeable odours.

Antiparasitics or *parasiticides* kill parasites infesting the surfaces of the body.

In dilute solutions most disinfectants act as antiseptics, yet many antiseptics while retarding the growth of micro-organisms do not act as efficient disinfectants, either because

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they become inert when they come in contact with organic matter, or are too poisonous to be used for a prolonged period. A large number of disinfectants, however, act upon most forms of living matter and are *general protoplasmic poisons* and have no specific action on microbes in preference to tissues. Therefore ordinary antiseptics while distroying microbes also cause damage to the tissues in which they are lodged. Since efficient disinfection also entails destruction of the surrounding cells, it is impossible to use a drug to disinfect the tissues of the body as a whole in sufficient concentration to destroy only the microbes without injuring the tissues.

An ideal disinfectant will exert a maximum action on the micro-organisms, *i.e.*, *parasitotropic*, and minimum action on the body tissues, should be soluble in water or will form a uniform emulsion in all proportions, rapid in action and non-corrosive to metals. Browning and his associates have shown that certain basic substances like flavine and acriflavine act more powerfully in the presence of serum, stimulate granulating processes, are not irritating to the tissues, and do not interfere with phagocytosis. These derivatives therefore are the nearest approach to ideal antiseptics.

The exact manner in which disinfectants act is not fully understood. The degree of ionisation of a solution may have an important bearing on its disinfecting efficiency. Disinfectants act in the following ways, *viz.*—(1) by physical means, these may be of different nature, (*a*) by abstracting water, *i.e.* salt action; (*b*) heat; (*c*) sunlight and ultra-violet rays; (2) by oxidation, as potassium permanganate, hydrogen peroxide, halogen compounds; (3) by acting as general protoplasmic poisons, *e.g.*, the coal-tar compounds, *etc.*; (4) by coagulating the proteins, *e.g.*, the heavy metals; and (5) by acting as reducing agents, *e.g.* SO_2. The action of mercury is due to its tendency to accumulate in the cell and on its surface by adsorption so that the microbe is surrounded by a dense layer of disinfectant (*see* mercury, page 449).

Antiseptics and disinfectants are classified as follows:—

Class A: General Antiseptics and Disinfectants
Class B: Intestinal Antiseptics (*see* page 331)
Class C: Urinary Antiseptics (*see* page 384)
Class D: Pulmonary Antiseptics (*see* page 306)
Class E: Parasiticides

Class A: General Antiseptics and Disinfectants

The drugs of this group are used for a wide variety of purposes. Apart from their use in surgical practice for disinfecting infected wounds, the skin, or to sterilise surgeon's hands and instruments, they have a greater field of usefulness in preventive medicine. To be of value the

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disinfectant must be used in solution or suspension in water and the strength should be such as will not cause much irritation of the tissues or the skin. For surface disinfection the oxidising disinfectants are sufficient to destroy the microbe, but for wounds it is necessary that the drug should penetrate into the tissues to reach the organisms, and this implies some destruction of the nervous structures and of the tissues in which they are imbedded causing certain amount of pain and irritation, consequently all efficient disinfectants are local irritants. Moreover some of them may be absorbed when applied to a large surface and exhibit poisonous symptoms. Owing to these effects it has been found that a wound heals less quickly when strong antiseptics are used and therefore their use is now confined only to those cases that are already infected, or there is possibility of infection, and no antiseptics are used in clean cases. In fact these heal more rapidly without the use of any antiseptics.

The general antiseptics are :—

1. Oxidising Agents
   Hydrogen Peroxide, Potassium Permanganate
2. Halogens and their Compounds
   Chlorinated Lime, Chloramine, Dakin's Solution, Eusol, Iodine, Iodoform
3. Heavy Metals
   Mercury (*see* page 444), **Silver Salts** (*see* page 117), **Copper Sulphate** (*see* page 123), **Ferrous Sulphate, Zinc Salts** (*see* page 121)
4. Coal-tar Compounds
   Phenol, Cresol, Resorcin, Trinitrophenol, Coal-tar, Tar, Betanaphthol, Salol, Coal-tar Dyes
5. Miscellaneous Compounds
   Formaldehyde, Acetone, Boric Acid, Borax, Oleum Hydnocarpi, Oleum Chaulmoogræ

1. Oxidising Agents

LIQUOR HYDROGENII PEROXIDI

Solution of Hydrogen Peroxide. H_2O_2

Source.—Prepared by the interaction of water, barium peroxide, and dilute sulphuric acid, at a temperature below 10°C. Contains 2·5 to 3·5 p.c. w/v of H_2O_2, corresponding to about ten times its volume of oxygen.

Characters.—A colourless, odourless liquid with a slightly acid taste. Renders saliva frothy. Rapidly decomposes on coming in contact with certain metals, oxidisable organic matter, also if allowed to become alkaline.

B.P. Dose.—30 to 120 ms. or 2 to 8 mils.

Non-official Preparation

1. **Magnesii Peroxidum.**—A white, tasteless powder. More stable than hydrogen peroxide. It is the chief active principle of **Magnesium Perhydrol**, which is useful in gastric and intestinal fermentation and indigestion. *Dose.*—15 to 60 grs. or 1 to 4 grms.

Pharmacology

Hydrogen peroxide is a powerful **antiseptic** and **disinfectant** by virtue of its oxygen which it gives off when brought

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into contact with many substances including all forms of living matter, pus, blood, bacteria, etc. It is not an irritant and being non-poisonous is largely used. Its effects, however, last only for a short time, for as soon as the oxygen is liberated it becomes inert. When injected directly into the blood it forms gas embolism causing death of the animal.

Therapeutics

Externally.—Hydrogen peroxide is largely used in general and dental surgery, also many cosmetics owe their efficacy to its presence. A solution (1 in 8) may be used with benefit in sores, foul suppurating wounds, chancres and fetid discharges from the ear.

Internally.—It is much employed as a gargle, or mouth wash, as in diphtheria, or pyorrhœa alveolaris, or for deeply furred tongue, and as a surgical cleanser in pus conditions. In pus cavities the oxygen is freed with great rapidity, and the pus corpuscles are said to be disintegrated.

POTASSII PERMANGANAS

Potassium Permanganate. $KMnO_4$

Source.—Obtained by the action of carbon dioxide on an aqueous solution of potassium manganate. Contains not less than 99 p.c. of potassium permanganate.

Characters.—Dark purple, slender, prismatic crystals, having a metallic lusture; odourless; taste, sweet, astringent. *Solubility.*—1 in 20 of cold water.

Incompatibles.—Iodides, organic substances and any reducing agent.

B.P. Dose.—1 to 3 grs. or 0.06 to 0.2 grm

Non-official Preparations

1. **Liquor Potassii Permanganatis.**—1 in 110 ms. Has a disagreeable taste. **Condy's fluid** is only of half the strength, and contains soda salt. *Dose.*—2 to 4 drs. or 8 to 15 mils.

2. **Calcium Permanganate.**—Crimson, deliquescent crystals; soluble in water. Useful in *enteritis* and *cholera*. *Dose.*—½ to 1½ grs. or 0.03 to 0.1 grm.

3. **Mangani Butyras, B.P.C.** *Syn.—Manganese Butyrate.*—1.5 c.c. of a 1 p.c. solution for injection intramuscularly at an interval of 3 to 4 days up to 3 injections. In staphylococcal, streptococcal and gonorrhœal infections, and in acne, boils, carbuncles, etc.

Pharmacology

Externally.—Potassium permanganate in its solid form is an irritant and even caustic, and in solution a stimulant. Apart from its local action on the human body, it is a valuable **oxidising agent**, giving off oxygen when moist and in the presence of organic matter, thus destroying decomposing ferments and septic germs. It is an **antiseptic, deodorant** and **disinfectant**. The only drawback is that it is expensive and yields up oxygen too quickly, rendering it inert after a short time; consequently its germicidal powers are limited.

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Internally.—It is an unstable compound, being decomposed into manganese dioxide in the stomach, in which form it is probably absorbed. Manganese has no direct hæmatinic property but is intimately related to iron metabolism specially in conjunction with copper, *i.e.* helps absorption of iron. When injected into the blood, or subcutaneously, it is excreted by the intestine and kidneys. Ringer considers it a useful emmenagogue.

Therapeutics

Externally.—For rapidly disinfecting stools and foul discharges, washing bed-pans, articles and hands after contact with infectious diseases, for flushing water-closets and drains, potassium permanganate in solution (1 in 150) is used as an antiseptic and deodorant. Being odourless and non-irritant, it is best suited for use at the bedside. Fabrics are stained by it, but the stain is easily removed by sulphurous acid; but they must be immediately washed, otherwise they would be damaged by the sulphuric acid formed. A weaker lotion (2 grs. to 10 ozs. of distilled water) can be used as a wash for foul or suppurating ulcers, abscesses, ozæna; or as a uterine or vaginal douche after parturition or in cancer of the os. Potassium permanganate is very largely used in the local treatment of gonorrhœa. Irrigations commencing with a strength of 1 in 8000 to 1 in 6000, and subsequently rising to 1 in 4000 or even 1 in 3000 are generally used. A saturated solution (1 in 20) is an excellent application in bites by poisonous snakes and rabid dogs, if it can be immediately applied. A 5 p.c. solution can also be freely injected into the subcutaneous tissues for this purpose, but it must be noted that its contact with the virus is essential, and therefore it is useless to try it some hours after the bite has been inflicted and when the virus has entered the circulation. Its use in the bites of poisonous snakes has been strongly advocated by Lauder Brunton and Rogers.

Internally.—Potassium permanganate makes a very effective gargle (2 grs. to 10 ozs. or the liquor diluted to 1 in 50) in foul and ulcerative diseases of the gums, mouth and throat. On account of its powerful oxidising property it is used to render certain poisons harmless, and therefore has been recommended in phosphorus, hydrocyanic acid, opium, morphine and other alkaloidal poisoning. As an emmenagogue it is recommended in delayed, deficient or arrested menstruation.

Injected into the body manganese acts as a powerful stimulant to the antibody formation, and manganese butyrate is largely used in the treatment of staphylococcal infections, such as boils, furunculosis, etc. Small doses are used in conjunction with iron in the treatment of microcytic anæmia.

Rogers strongly urges the administration of a drink of

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calcium permanganate gr. 4 to one pint of boiled water in cholera. It may be given *ad libitum*, at the same time he administers pills of 2 grs. of potassium permanganate, made up with kaolin and coated with salol, every ½ hour until the stools become greenish in colour, and then at longer intervals. This treatment combined with injection of hypertonic saline solution has yielded brilliant results.

It can be given in pill or solution. There is a danger of ulceration being caused by the tablets. Liquor Potassii Permanganatis is disagreeable to swallow.

2. Halogens and their Compounds

Chlorine, Bromine, Iodine, Iodoform

CALX CHLORINATA

Chlorinated Lime

Syn.—Bleaching Powder. Chloride of Lime.

Source.—Obtained by the action of slaked lime upon chlorine. Contains not less than 30 p.c. of chlorine.

Characters.—A dull, white powder with a characteristic smell. Becomes moist and gradually decomposes on exposure to air.

Solubility.—Partly in water.

Non-official Preparations

1. **Liquor Acidi Hypochlorosi Co.** *Syn.—Eusol.*—Contains approximately 0.27 p. c. hypochlorous acid with small amounts of calcium biborate and calcium chloride. To 1 litre of water add 12.5 grms. bleaching powder, shake vigorously, add 12.5 grms. boric acid powder and shake again, allow to stand for some hours, then filter off.

Note.—Keep in stoppered bottles away from light. Deteriorates in hot weather after one week.

2. **Pulvis Calcis Chlorinatæ et Acidi Borici.** *Syn.—Eupad.*—Mix intimately equal weights of finely ground bleaching powder (dry) and powdered boric acid. Contains 15 p. c. available chlorine, or 11 p.c. (approximately) of hypochlorous acid. Can be used as a dry dressing. The gas evolved acts more powerfully than Eusol, especially when moistened betweeu layers of gauze or lint and covered with wool and bandaged.

3. **Dichloramina, U.S.P.** *Syn.—Dichloramine-T.*—Contains 28 to 30 p.c. of active chlorine. Gradually decomposes and loses chlorine on exposure to air. Pale yellow crystals or yellow crystalline powder with odour of chlorine. Almost insoluble in water.

4. **Liquor Chlori (Burney Yeo).**—Put powdered potassium chlorate 30 grs. into a 12 oz. bottle and pour over it strong hydrochloric acid 1 dr., cork, shake, and allow gas to generate, then add water by degrees, shaking after each addition. Into this solution dissolve 24 to 26 grs. of quinine and 1 oz. of syrup of orange peel. *Dose.*—1 oz. every 3 or 4 hours in *typhoid fever.*

CHLORAMINA

Chloramine. $C_7H_7O_2NClSNa.,3H_2O$

Syn.—Chloramine-T.

Source.—It is sodium *p*-toluenesulphonchloroamide. Prepared by the limited action of solution of sodium hypochlorite upon *p*-toluene sulphonamide.

Characters.—White crystals, or crystalline powder; odour, that of chlorine; taste, unpleasant, bitter. Effloresces and slowly decomposes on exposure to air, losing chlorine and assuming a yellow

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colour. *Soluble* in about 7 parts of water, in 2 parts of boiling water, and in 12 parts of alcohol (90 p.c.).

LIQUOR SODAE CHLORINATAE CHIRURGICALIS

Surgical Solution of Chlorinated Water

Syn.—Dakin's Solution.

Source.—Prepared by combining chlorinated lime, sodium carbonate, boric acid and distilled water in proper proportions indicated in the B. P. Contains not less than 0.5 p.c. w/v and not more then 0.55 p.c. w/v of available chlorine.

PHARMACOLOGY

Externally.—Chlorine has a great affinity for hydrogen, and consequently decomposes chemical and organic compounds which contain it, such as ammonia, sulphuretted hydrogen, and many organic matters. It is a powerful poison to all living matter and bacteria, but since it is a violent irritant it is not used in surgical practice except in the form of different compounds which give off chlorine more slowly. Applied to the skin for a long time, as in the case of workmen in a manufactory of bleaching powder, it causes itching, redness and inflammation, leading even to vesication or sloughing. Inhaled in a concentrated form it is a powerful irritant to the respiratory passages and may cause death from spasm of the glottis or inflammation of the air-passages.

All these compounds are highly efficient disinfectants and deodorants and part with their available chlorine in a few minutes in the presence of excess of proteins, consequently their disinfectant action is very rapid. This action is a simple chemical reaction. The chlorine combines with all forms of proteins specially the amine groups forming chloramine which is a powerful antiseptic and kills any micro-organisms with which it comes into contact; but if there is an excess of protein the available chlorine is rapidly exhausted and it ceases to have any antiseptic or disinfectant property. The chloramines so formed being soluble, the hypochlorites dissolve organic matter and dead tissues. The relative action of the different preparations depends on their content of available chlorine. Chloramine solutions are more stable, neutral, less irritating and more efficacious as they do not give up the whole of the available chlorine as rapidly as the others.

Internally.—It exerts the same local influence on the parts with which it comes in contact, until decomposed into chlorides in the stomach, when it loses its virtues as an uncombined element.

THERAPEUTICS

Externally.—As a *disinfectant* and *deodoriser*, chlorinated lime is often poured into drains, privies, urinals, bed-pans,

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etc. Moistened with water it may be put in saucers in different parts of a sick-room to disinfect the air. If the room requires a speedy disinfection, chlorine gas may be quickly generated by pouring sulphuric acid on salt and black oxide of manganese, the room being closed up for 24 hours. The chlorine thus liberated attacks the hydrogen of the ammonia and sulphuretted hydrogen present in the atmosphere of the room.

Chlorinated lime and liquid chlorine are largely used for sterilising drinking water and swimming baths. One drachm of bleaching powder dissolved in a pint of water and a teaspoonful of this will purify two gallons without imparting any taste to the water. For swimming baths the concentration necessary to keep the water pure is 0.2 part per million.

Eusol, Chloramine-T, and Dakin's solution are largely used as non-irritating and inexpensive antiseptics for wounds and ulcers, and for washing cavities with foul discharges, and as a nasal or vaginal injection, etc. All these compounds contain active chlorine. Since the chlorine or hypochlorite is rapidly used up by contact with the proteins of the inflamed surface, continuous saturation of wounds is necessary, and this will abolish sepsis, dissolve dead tissue and promote healing. Dakin's solution is one of the most suitable and stable forms of chlorine for this purpose.

Internally.—The different solutions are used as gargles (chloramine 0.5 p.c.) in malignant sore throat, diphtheria, mercurial salivation, and sloughing stomatitis. A solution of chlorine is recommended in septic diseases, such as typhoid fever and septicæmia, but the results are not encouraging. Burney Yeo's chlorine mixture has not proved successful in our hands, though it relieves flatulence. The great drawback to its use is its extremely nauseous taste.

IODUM

Iodine

Source.—Obtained from naturally occurring iodides and iodates.

Characters.—Heavy, bluish-black, brittle, rhombic prisms or plates, with a metallic lustre; odour, characteristic. Volatilises at ordinary temperature. *Slightly soluble* in water, more in alcohol (90 p.c.), soluble in chloroform, ether, glycerin and carbon disulphide. Freely in solutions of iodides.

Incompatibles.—Alkalies and alkaline carbonates, oil of turpentine, most volatile oils, tannin and vegetable astringents.

Official Preparations

1. **Liquor Iodi Fortis.** *Syn.—Tr. Iodi Fort.; Lint. Iodine.*—Contains 10 p.c. w/v of iodine, and 6 p.c. w/v of potassium iodide.

2. **Liquor Iodi Mitis.** *Syn.—Tr. Iodi Mitis; Tr. Iodi.*—Contains 2.5 p.c. of iodine and 1.5 p.c. of potassium iodide, or about $\frac{1}{5}$ gr. of iodine (1 gr. total iodine) in 30 ms. **B.P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

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3. **Liquor Iodi Simplex.**—Contains approximately 10 p.c. w/w of total iodine, or 1½ grs. in 15 ms. **B.P. Dose.—3 to 15 ms. or 0.2 to 1 mil.**

4. **Syrupus Ferri Iodidi.**—Contains 7½ grs. of ferrous iodide, equivalent to 1⅛ gr. of iron in 120 ms. **B.P. Dose.—30 to 120 ms. or 2 to 8 mils.**

Non-official Preparations

1. **Liquor Iodi Co. U.S.P.** *Syn.—Lugol's Solution.*—Iodine 5, pot. Iodide 10, water *q.s.* to 100. Useful in *exophthalmic goitre*, reduces the basal metabolic rate. *Dose.*—0.2 c.c. or 3 ms.

2. **Liquor Iodi Decoloratus, B.P.C.**—Iodine 2.85, Rectified Spirit 28.6, Strong Solution of Ammonia 62.5, Alcohol (90 p.c.) to 1000.

3. **Pigmentum Iodi Co., B.P.C.** *Syn.—Mandl's Paint.*—Iodine 2 drs., pot. iodide 4 drs., oil of peppermint 72 ms., aqua ½ oz., glycerin to 20 oz.

4. **Entodon.**—*Hexamethyl - diamino - isoproponal - di - iodide.*—A water-soluble iodine preparation. Used either *subcutaneously* or *intravenously*. *Dose.*—½ to 1 ampoule or 1 to 2 c.c.

Pharmacology

Externally.—The action of iodine is identical with that of chlorine, *i.e.*, it unites with amine group of proteins, with this difference that iodamines are insoluble and being less volatile, iodine is a slower bactericide than chlorine, though more lasting. Its inhalation produces irritation of the respiratory passages, cough, sneezing, frontal and thoracic pain and dyspnœa. It is a powerful **antiseptic, disinfectant** and **antiparasitic.** As an antiseptic it is superior to perchloride of mercury. It does not coagulate proteins, or form inert compound with tissues, possesses greater penetrating power, and is more stable specially when iodide is added to the solution. On the skin it is an **irritant, rubefacient** and **vesicant,** according to the strength and length of application. It stains the skin yellowish brown and deadens the cuticle which peels off. Owing to the lasting irritation of the skin there is some congestion of the subcutaneous tissues which aids absorption of exudation.

Internally.—In the stomach and intestines iodine is slowly converted into iodide and absorbed as such, but much may be left free to cause vomiting, purging and colic. It therefore produces the usual effects of iodide. It is taken up by the spleen, lymphatic glands and to a less extent by the liver. It is excreted with the urine, milk, sweat and bronchial mucus. In poisoning, gastro-enteritis may cause death from collapse and failure of heart and respiration. In minute doses it occasionally stops vomiting

Dry thyroid contains 0.01 to 1.16 p.c. of iodine, while other tissues contain less than 0.001 p.c. It exists in the thyroid gland as *thyroxine* and its deficiency either in the food or water produces goitre which may be improved either by the use of iodine or iodides.

Toxic action.—It is generally taken in the form of tincture. Soon

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after swallowing there is uneasiness of the stomach with a disagreeable metallic taste followed by vomiting and severe abdominal pain. If the dose is large the pulse becomes feeble and collapse sets in. Diarrhœa follows, and the stool may contain blood. The vomit may be of iodine colour, and if the patient has taken starchy food, blue. Fatal cases are due to injection of too large quantities into serous cavities.

Treatment.—Evacuation. Demulcent drinks, chiefly starch, *e.g.* arrowroot or cooked flour. Eggs, milk and large quantities of alkalies in dilute solutions to fix the iodine. 5 p.c. solution of sodium thiosulphate may also be used. In poisoning due to injection into cysts, hydrocele, etc., very little can be done.

THERAPEUTICS

Externally.—Iodine is locally applied in subacute and chronic inflammation of joints, synovial membranes, lymphatic glands, pleura, etc. Its effects are mainly due to a mild irritant action which helps absorption of inflammation or exudation of underlying tissues or organs like other counter-irritants. Liq. iodi mitis has been successfully injected into cysts and hydroceles to induce an inflammation and adhesion of the walls and thus obliterate their cavities. Liq. iodi fortis being very strong cannot be painted more than twice or at the utmost thrice over the same spot. If the application causes much pain and irritation, the iodine can be washed off with alcohol, or with a solution of potassium iodide. It is used for the **sterilisation of the skin** before operations of all kinds when it penetrates readily into the pores and has a powerful germicidal action. Iodized phenol is a valuable local application in endometritis. Vapour Iodi Ætherealis (iodine 3 gr., ether 2 dr., phenol 2 dr., creosote 1 dr., alcohol (90 p.c.) 3 dr.), is an efficacious inhalation in chronic bronchitis and phthisis. Being antiparasitic, the mild liquor is painted over ringworm with benefit, though it causes some burning.

Internally.—The weak solution painted over the gums and teeth dissolves tartar, heals ulcers, and stimulates the growth of gums, when they have ulcerated and receded. Iodine gargle (2 to 4 drs. in water 8 ozs.) checks mercurial salivation, and heals syphilitic and non-syphilitic sores of the mouth and throat. Pigmentum Mandl is a capital application for chronic granular pharyngitis. Liquor iodi mitis, 1 or 2 drops in 1 oz. of water, at times checks vomiting, when given every fifteen minutes. Iodine has been recommended in scrofula, malarial fever and gout, but without any appreciable benefit.

Iodine is used intravenously in various diseases, chiefly plague, erysipelas, septic wounds and other streptococcal infections with much success. The usual formula is iodine gr. 24, pot. iodide gr. 36, distilled water to 1 oz.; 1 c.c. being equal to 1 gr. iodine. The injections are commenced with 1 c.c. and then worked up to 5 c.c. by increasing ½ to 1 c.c.

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with each injection, and are given once a week or oftener if necessary. The untoward symptoms are a rise of temperature, pain and sometimes local thrombosis.

In the form of Lugol's solution (10 ms. three times a day), or liquor iodi simplex (5 ms. increased to 20 ms. by 1 minim per dose per day, three times a day in milk), it has been used in **exophthalmic goitre** apparently with some benefit. It improves nervousness, promotes sleep and appetite, slows the heart, and reduces the basal metabolism by 25 to 30 p.c. The results are not permanent for after a few weeks the symptoms return even though the treatment is continued. It is useful in that it makes the patient fit enough for surgical interference. In place of iodine, iodides may also be used. The relation of iodine in the formation of endemic goitre has led to the use of food rich in iodine, or iodised salt, as a prophylactic against the disease in endemic areas. But this treatment has been given up in favour of iodides and thyroid.

The use of nascent iodine has been advocated in the treatment of **pulmonary tuberculosis.**

Iodine compounds being opaque to X-rays have been used for purposes of diagnosis where bismuth or barium are inadmissible. The preparations used for the purpose are either dissolved in oil, as lipiodol, or water soluble compounds, as uroselectan.

IODOFORMUM

Iodoform. Tri-iodomethane. CHI_3

Source.—Prepared by the action of iodine on acetone in the presence of alkali.

Characters.—Shining, lemon-yellow, small, hexagonal crystals, unctuous to the touch with a characteristic, persistent and disagreeable odour and taste. Volatilises slowly. Contains not less than 99 p.c. CHI_3. *Solubility.*—Slightly in water, 1 in 8 of ether, 1 in 10 of chloroform, 1 in 100 of alcohol (90 p.c.), fixed and volatile oils. Sparingly in benzene.

B.P. Dose.—$\frac{1}{2}$ **to 3 grs. or 0.03 to 0·2 grm.**

Official Preparations

1. **Suppositorium Iodoformi.**—3 grs. or 0.2 grm. in each.
2. **Oculentum Iodoformi.**—Iodoform 4 p.c.

Non-official Preparations

1. **Collodium c. Iodoformo.**—Iodoform 1, Collodion 12. As a pigment in *venereal sores* and *glandular swellings.*
2. **Emulsio Iodoformi.**—Iodoform 10, Glycerin 70, Water 20. For injection into *sinuses* and *abscess cavities.*
3. **Iodoform Varnish.** *Syn.—Whitehead's Paint.*—Contains iodoform 10 p.c. in Tr. Benzoini Co., in which ether is substituted for alcohol.

Substitutes for Iodoform

1. **Thymolis Iodidum.** *Syn.—Aristol.*—Prepared by the interaction of iodine and thymol. Contains 43 p.c. of iodine. A reddish-brown powder insoluble in

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water and glycerin, but soluble in collodion, ether, and oils. Useful in *ulcerative lupus, tinea, eczema, psoriasis,* when applied as an ointment (10 p.c.) or dusted, or in collodion.

2. **Iodol.** *Syn.—Tetra-Iodo-Pyrrol.*—A brownish-white powder without disagreeable smell and toxic action, insoluble in water, but soluble 1 in 145 of glycerin, alcohol, chloroform, and ether. Externally it acts like iodoform, and internally like potassium iodide. *Dose.*—1 to 3 grs. in pill or capsule.

3. **Calcii Iodobehenas, U.S.P.** *Syn.—Sajodin.*—An organic compound with calcium and iodine 23·5 p.c. *Dose, U. S. P.*—0.5 gm. or 8 grs.

Pharmacology

Externally.—Iodoform has no special action on the skin or mucous membrane, but in susceptible persons it acts as an irritant and causes eruption to appear near the seat of the application. It is a local **anæsthetic, antiseptic, disinfectant** and **deodorant**. Pure dry iodoform is not an antiseptic and in solution it is very unstable. Since cultures of bacteria grow even in the presence of iodoform, the antiseptic action is due to the formation of iodine which is slowly evolved when it comes in contact with tissues or their extracts, particularly with diseased tissues. The iodine is liberated in an amount which does not irritate the wound, but is sufficient to prevent the growth of micro-organisms.

Internally.—The precise action of iodoform within the body is not fully understood. It is decomposed in the presence of alkaline fluids and in protein solutions, and the liberated iodine combines with the alkalies of the fluids to form iodides. After absorption iodine has been found in the saliva, sweat and bronchial secretions. But it is chiefly as iodides and partly in organic combination that iodoform is excreted in the urine. It is excreted very slowly and traces of iodides have been found for more than a month after the administration of the drug.

The symptoms of poisoning are complex and varied. A portion of iodoform circulates unchanged and gives rise to the cerebral symptoms; while other symptoms are due to the presence in the blood and tissues of iodine and iodides. The acceleration of the heart and other symptoms are due to the over-activity of the thyroid.

Toxic action.—Acute poisoning is rare now. Chronic poisoning may take place either from repeated doses, or through absorption from a raw surface. The symptoms are malaise, vertigo, dilatation of the pupil, loss of appetite, gastro-intestinal disturbance, quick, feeble pulse, fever (temperature sometimes rising to 104°F.), delirium, mania, or melancholia, erythema and perhaps eczema (iodoform dermatitis), convulsion, collapse and at times death. Fatty degeneration of the liver and muscles, hæmaturia, and albuminuria sometimes occur. These symptoms may come on suddenly, or may develop gradually, lasting for weeks. Some persons are specially susceptible to iodoform.

Treatment of iodoform poisoning.—When slight, the symptoms disappear on withdrawal of the drug. In more serious cases the symptoms appear so late that removal of the poison will not avert a fatal result. Sodium bicarbonate gr. 15 every hour prevents the

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formation of free iodine. Milk of magnesia 1 dr. every three hours until bowels move should be given and then once every day to keep the intestines active. Pot. brom. gr. 20 in half a tumbler of water followed by four 10 gr. doses hourly will antagonise cerebral excitement and help elimination.

Therapeutics

Externally.—Iodoform is employed as a local antiseptic, but the strong characteristic smell is the chief drawback to its use. It is extensively employed in surgery in various forms such as bismuth iodoform paste, or as powder, ointment, emulsion, bougie, gauze, etc., in wounds, sloughing sores, syphilitic and scrofulous ulcers, chancres, abscess cavities, sinuses, fistulæ, etc. Collodion iodoform subdues mumps, buboes and chronic glandular enlargements. The suppository is used to relieve painful conditions of the bladder and rectum and the ointment gives great relief in **pruritus ani.** It may be insufflated for otorrhœa and frequently proves extremely beneficial.

Internally.—It is rarely used internally. As a spray, pastil or insufflation, it is used in syphilitic sores of the mouth, tubercular pharyngitis, and laryngitis. It has been unsuccessfully used in gastric ulcers and phthisis; and Burney Yeo recommends ½ gr. dissolved in cod-liver oil three times a day in tubercular peritonitis of children.

3. Coal-tar Compounds

PHENOL

Phenol. C_6H_6O

Syn.—Acidum Carbolicum; Carbolic Acid; Phenyl Alcohol.

Source.—Obtained from coal tar oil, or prepared synthetically.

Characters.—Small, colourless, needle-shaped, deliquescent crystals, becoming pinkish when exposed to moist air; odour, peculiar, but not tarry; taste, sweetish, pungent. *Solubility.*—1 in 13 of water, freely in glycerin, ether, chloroform, fixed and volatile oils, and alcohol.

B.P. Dose.—1 to 3 grs. or 0.06 to 0.2 grm.

Official Preparations

1. **Phenol Liquefactum.** *Syn.—Acidum Carbolicum Liquefactum.*—Contains 80 p.c. w/w of phenol. A colourless liquid, becoming pinkish on keeping. Characteristic, somewhat aromatic odour. Caustic. **B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.**
2. **Trochiscus Phenolis.**—Each contains approximately 0.03 grm or ½ gr. of phenol.
3. **Glycerinum Phenolis.**—16 p.c. phenol. **B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**
4. **Suppositorium Phenolis.**—1 gr. (0.06 G.) in each.
5. **Unguentum Phenolis.**—Phenol 3 p.c.

Non-official Preparations and Derivatives

1. **Sodii Phenolsulphonas.** *Syn.—Sodium Sulphocarbolate.*—In colourless, transparent, rhombic prisms with a saline bitter taste. Soluble in 5 parts of water.

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Antiseptic and *antipyretic*. In *diphtheria*, *cholera* and *septic fever* and in *tympanites* in preference to carbolic acid. *Dose.*—5 to 15 grs. or 0·3 to 1 grm.

2. **Phenol Camphor.**—Phenol 1, Camphor 3. As a local anæsthetic for toothache.

3. **Phenol Iodisatum, B.P.C.** *Syn.—Iodised Phenol.*—Iodine 1, Liquefied Phenol 10. Caustic.

4. **Bromol.** *Syn.—Tribromophenol.*—A white, crystalline, insoluble salt, prepared by mixing a solution of carbolic acid with bromine water. A powerful antiseptic and caustic. Internally in typhoid fever and diarrhœa. *Dose.*—½ to 2 grs. or 0.03 to 0.12 grm.

5. **Acidum Trichlorphenicum.** *Syn.—Trichlorphenol.*—Insoluble acicular crystals, forming soluble salts with alkaline bases. Twenty-five times stronger than carbolic acid.

Pharmacology

Externally.—Outside the body carbolic acid arrests the life-processes of the lower organisms, both vegetable and animal, and is a powerful parasiticide. It destroys also the properties of organised ferments, as yeast, moulds and bacteria, and prevents the zymosis of septic germs. Hence it is an antizymotic and disinfectant, though not so powerful as corrosive sublimate. As it prevents decomposition and generation of foul-smelling gases, it is an antiseptic and deodorant. Coming in contact with the serum it precipitates proteins, and being rapidly soluble in lipoids it has a greater penetrating power than many other antiseptics. It is an efficient bactericide, and in concentrations varying from 1 in 30 to 1 in 200 it kills most bacteria. Spores are more resistant to its action, so that a 5 p.c. solution takes two days to kill the spores of anthrax. Since phenol has greater affinity for oil than for water or solutions of salts in the tissues, oily solutions are less antiseptic. On the other hand its activity is increased by the addition of sodium chloride which reduces its solubility and thus helps its concentration in the micro-organisms.

Applied to the skin it is absorbed by the unbroken skin but more from a mucous surface, and causes a temporary burning and tingling followed by anæsthesia. Stronger applications act as caustic, with the formation of a white eschar without vesication. Hence, it is a local **irritant, anæsthetic** and **escharotic.**

Internally. **Gastro-intestinal canal.**—In a concentrated form carbolic acid has a similar action on the mucous membrane of the mouth, fauces, œsophagus and stomach, as on the skin. It is a powerful gastro-intestinal irritant. It is readily absorbed from the stomach and the intestine, therefore it cannot act as an intestinal antiseptic. Unorganised or chemical ferments (*enzymes*), such as pepsin, ptyalin, are not so readily affected by it except in very large doses.

Blood and circulation.—Phenol increases the rate of the heart, due probably to direct action on the cardiac muscle or on the nerves. This acceleration was formerly believed to be due to increased muscular movement and

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convulsions, but this view is now found to be incorrect. The heart is subsequently slowed. Injected directly into the blood it depresses the vaso-motor centre. This effect combined with the weakness and slowness of the heart causes the blood-pressure to fall. Although carbolic acid added to defibrinated blood leads to the slow formation of methæmoglobin, this change does not occur in the living animal.

Respiration.—No effect is seen in small doses, but large doses first stimulate then paralyse the respiratory centre making the respiration slow and shallow.

Temperature.—No effect is produced by medicinal doses but large ones lower it possibly due to collapse. It is not certain whether fall of temperature is aided by some changes in the regulating mechanism.

Nervous system.—In fairly large doses it affects the medulla and cerebrum. Its influence on the respiratory, cardiac and vaso-motor centres has already been referred to. It also stimulates the salivary and sweat centres, producing salivation and perspiration. The cells of the anterior cornua are first stimulated then paralysed, the result being convulsion followed by paralysis. Poisonous doses produce headache, giddiness, contracted pupils and finally coma.

Urine.—Carbolic acid is chiefly excreted by the urine in the form of pyrocatechin and hydroquinone. Pyrocatechin being a dark-coloured body gives it a *dark* or *olive-green* colour but this cannot be the sole cause. The unoxidised portion combines with H_2SO_4 and is excreted as phenyl sulphuric acid which is inert. Sometimes albumin is detected. *In poisoning* by phenol, *the normal sulphates disappear from the urine.* The glycuronates reduce Fehling's solution and the urine therefore gives rise to the suspicion of diabetes. The urine in these cases resists decomposition for a considerable time.

Elimination.—By the saliva, sweat, respiratory and gastro-intestinal secretions and urine. A portion of it is lost in the body.

Acute toxic action.—If swallowed in a concentrated form the patient feels intense burning pain in the mouth, fauces and stomach, with the formation of white eschars in the mouth, etc. He soon becomes collapsed with a cold clammy sweat, subnormal temperature, weak, feeble pulse, and shallow laboured breathing, heart and respiration stopping almost simultaneously. Reflex excitability is lost and convulsions occasionally set in. Urine becomes dark green, and finally the patient becomes insensible and comatose. Small doses cause nephritis with albumin in the urine. The *post-mortem* reveals hard, white eschars in the mouth, œsophagus and stomach with or without inflammatory redness. Blood becomes dark and its coagulability is diminished.

Antidotes.—Pump, emetics. Wash out the stomach. If necessary add 10 p.c. alcohol to water which dissolves the poison more readily and helps its removal. Washing must be continued till the phenol odour disappears because quite a large quantity remains in the stomach without absorption. If coma sets in, artificial respiration,

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caffeine and strychnine to sustain the heart. Chalk, saccharated lime, egg albumin, oils, demulcents, stimulants, hot water bottle, etc., are useful adjuvants.

Chronic toxic action.—The following symptoms have been observed by the writer in a case where a deep suppurating cavity in a scrotal elephantiasis was plugged with carbolic acid dressings, *viz.*, headache, anorexia, gastro-intestinal disturbance, insomnia, fever, dark urine.

Caution.—Green or smoky urine is often the first warning but in a doubtful case the urine should be examined to ascertain the presence or absence of ordinary sulphates. The products of carbolic acid in the urine can be detected by distilling the urine, and adding bromine water to the distillate, when white crystalline sulphocarbolate precipitates.

THERAPEUTICS

Externally.—Crude phenol is employed to disinfect and remove the foul odours of water-closets, drains, dissecting room, hospital-wards, bed-pans, spittoons, etc. For small operations, as for instance, puncturing the skin with a hypodermic needle, phenol may be applied to produce local anæsthesia. To stimulate indolent sores, to prevent the foul smell of gangrenous ulcers, to destroy exuberant granulations, condylomas and the poison of poisoned wounds, the application of undiluted phenol is most valuable. A 20 or 40 p.c. solution allays the itching of urticaria and eczema. To wash surgeon's hands, instruments, sponges, linen, and parts to be operated upon, carbolised lotions were extensively used in surgical practice, but its use has become very much restricted in recent years. ½ gr. in water 5 ms. removes piles when injected. It is doubtful whether its inhalation is of any service in phthisis, gangrene of the lungs and chronic bronchitis. The application of Phenol Camphor or Iodised Phenol relieves excoriation and ulceration of the os and cervix and chronic endometritis. A vaginal douche (1 in 80 or 100) is beneficial in leucorrhœa, uterine ulcers and cancer, but it sometimes causes itching and irritation.

Internally.—For ulcerative and aphthous stomatitis, follicular tonsillitis and diphtheria the glycerin may be used as a paint, or a lotion (glycerin phenolis 15 to 20 ms. in water 1 oz.) may be used as a gargle. Subcutaneous injections of 2 to 3 p.c. aqueous solution, given every four hours were at one time extensively used in the treatment of tetanus. As an intestinal antiseptic, phenol has been employed in enteric fever, sloughing dysentery, acute and chronic diarrhœa, but with doubtful results.

Prescribing hints.—Best given in pills. They must be coated with keratin or varnished with salol if intended for action on the intestine. When given in a mixture it should be well diluted and combined with glycerin and peppermint water.

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CRESOL

Cresol. C_7H_7OH

Syn.—Acidum Cresylicum ; Cresyl Hydrate.

Source.—A mixture of cresols and other phenols, obtained from coal-tar.

Characters.—An almost colourless to pale brownish-yellow liquid, becoming darker on keeping, or on exposure to light. Soluble in 50 parts of water, solution being neutral, freely soluble in alcohol (90 p.c.), in ether, chloroform, glycerin and in the fixed and volatile oils. Sp. gr. 1.035 to 1.050.

B.P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

Official Preparation

1. **Liquor Cresolis Saponatus.** *Syn.—Lysol.*—50 p.c.

Pharmacology and Therapeutics

Cresol is a mixture of ortho-, meta-, and para-cresols. The effects produced by the cresols are the same as those of phenols. Meta-cresol being the least poisonous and a more efficient germicide than carbolic acid may be used in the form of lotions and ointments in place of phenol. Liquor cresolis saponatus may be used as an antiseptic lotion for washing surgeon's hands, abscess cavities, etc. Cresol preparations are largely used in obstetrical and gynæcological practice. In the form of vapour it is used in whooping cough, and other respiratory troubles, the atmosphere of the room being rendered saturated with the vapour. *Internally* it is used in keratin-coated capsules as an intestinal antiseptic but its action as such is doubtful. It is a cheap and powerful disinfectant, less poisonous than both phenol and mercurials and therefore more suitable for general use, but loses 50 to 70 p.c. of its power when it comes in contact with organic matter.

RESORCINOL

Resorcinol. $C_6H_6O_2$

Syn.—Resorcin. Meta-dihydroxy-benzene.

Source.—Obtained by the interaction of sodium hydroxide and sodium *m*-benzene-disulphonate.

Characters.—Colourless, or nearly colourless, acicular crystals or powder. Faint odour ; taste, pungent and sweetish, followed by bitterness. *Solubility.*—In less than 1 part of water, in 1 part of alcohol (90 p.c.), in ether, glycerin, and olive oil.

B.P. Dose.—1 to 5 grs. or 0.06 to 0.3 grm.

Non-official Preparations

1. **Spiritus Resorcinolis, B.P.C.** *Syn.—Spiritus Capillaris.*—Resorcin 2.50, Castor Oil 2.50, Spirit of Cologne 20, Alcohol (90 p.c.) to 100. Used in dandruff and alopecia.

2. **Resorcin Monacetate.** *Syn.—Euresol.*—A honey-like mass, available for all purposes for which resorcin is used, especially for application to those parts of the skin covered with hair.

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3. **Thio-resorcin.**—A compound of resorcin and sulphur. A yellowish powder, recommended as a *substitute for iodoform*. A 5 p.c. ointment in skin diseases.

Action and Uses

Resorcin is an antiseptic stronger than phenol, but less poisonous. It is used as a lotion or ointment (20 grs. in 1 oz. of zinc ointment) in psoriasis, eczema, and other irritable skin affections, as gargle in stomatitis, as spray in diphtheria and whooping cough, and as paint (10 grs. in glycerin 1 oz.) in sore-throat. Andeer's lotion (resorcin 1 in water 10) is a useful application in psoriasis and chronic eczema.

Internally.—It acts as an intestinal antiseptic and is used in infantile diarrhœa, especially in combination with benzo-naphthol. It is said to have a specific action comparable to quinine and has been used in hectic fevers. It should be administered well diluted with water and flavoured with syrup of orange. On account of the readiness with which it forms methæmoglobin and the danger of collapse, it should be used with caution. It is incompatible with alkalies and spirit of nitrous ether.

TRINITROPHENOL

Trinitrophenol

Syn.—Picric Acid.

Source.—Obtained by treating phenol with sulphuric acid at a suitable temperature, and by treating the product with nitric acid. Contains not less than 99 p.c. of tri-nitro-phenol.

Characters.—Bright yellow crystalline powder. Inodorous; taste very bitter. *Solubility.*—In 90 parts of water and in 10 parts of alcohol (90 p.c.).

B.P. Dose.—1 to 5 grs. or 0.06 to 0.3 grm.

Non-official Preparations

1. **Ammonii Picras.**—In yellow scales. Soluble in water. Useful in *ague* and *malarial fevers*. *Dose*—1/6 to 1/3 gr. or 0.01 to 0.02 gm.
2. **Unguentum Trinitrophenolis, B.P.C.**—Picric acid 2, water 2, soft paraffin 96.

Pharmacology and Therapeutics

Picric acid is an irritant to the skin and mucous membranes. In large doses it causes vomiting and often anuria and strangury. After absorption it colours the skin and mucous surfaces yellow, simulating jaundice, due to the staining of the epithelium by the acid. The saturated solution is used as a hardening agent in microscopical work. When heated with glucose it is reduced to picramic acid, and this test is utilised in the detection and estimation of glucose in urine (Johnson's test); with citric acid it forms the well known Esbach's test for albumin in urine.

It is a protoplasmic poison and precipitates proteins and acts as an antiseptic and is four times more active than phenol.

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Its chief therapeutic use is in cases of burns and scalds. The wounds heal under the superficial scab formed. Lint or cotton-wool soaked in 1 p.c. solution of the acid is generally used for the purpose. A 5 p.c. solution in alcohol hardens the skin and checks local sweating and is recommended for hyperidrosis of the feet. The ointment may be used in eczema, pruritus, etc.

The stains are removed by first applying powdered potassium sulphate for a minute and then washing with soap.

PIX CARBONIS PRAEPARATA

Prepared Coal Tar

Syn. I.V.—*Alkatra*, Beng.

Source.—Prepared by heating commercial coal tar in a shallow vessel and maintaining it at 50°C. for one hour, stirring constantly.

Characters.—A nearly black, viscous liquid, brown in very thin layers; heavier than water. Strongly empyreumatic, characteristic odour. Almost entirely soluble in benzene and in chloroform; partially in alcohol (90 p.c.), very slightly in water.

Composition.—(1) *Benzene* and homologous hydrocarbons. (2) *Phenol.* (3) Cresols, naphthalene, anthracene, etc.

Official Preparation

1. **Liquor Picis Carbonis.**—20 p.c. Is the official imitation of **Liquor Carbonis Detergens** which is an alcoholic solution of common coal tar.

Pharmacology and Therapeutics

The action and uses of prepared coal tar are identical with those of wood tar except that the former is scarcely used internally. Liquor carbonis detergens is the best known remedy for chronic eczema. An ointment containing liquor carbonis detergens 0.5 dr., liq. plumbi subacetatis 0.5 dr., white precipitate 15 grs., soft paraffin 1 oz. is useful for the same purpose.

PIX LIQUIDA

Tar

Syn.—Wood Tar; Pix Pini, U.S., Pine Tar; Stockholm Tar.

Source.—A bituminous liquid obtained from the wood of various trees of the family *Pinaceæ* by destructive distillation.

Characters.—A dark brown or blackish, semi-liquid substance. Odour, peculiar, aromatic. Empyreumatic taste and acid reaction. *Solubility.*—1 in 10 of alcohol (90 p.c.), slightly in olive and turpentine oils.

Composition.—(1) *Cresol.* (2) *Phenol.* (3) *Guaiacol.* (4) *Pyrocatechol.* (5) *Toluene.* (6) *Xylol.* (7) *Acetone.* (8) *Resins*, etc.

B.P. Dose.—2 to 10 grs. or 0.12 to 0.6 grm.

Non-official Preparations

1. **Syrupus Picis Liquidæ.**—Tar 5.0 grm., sugar 850 grm., alcohol (90 p.c.) 52·5 mil., water to 1000 mils. Used in *winter cough*, *phthisis* and *chronic bronchitis*. *Dose.*—2½ drs. or 10 c.c.

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2. **Unguentum Picis Pini, U.S.P.**—Tar 50, yellow wax 15, petrolatum 35. Melt and mix.

Pharmacology

Externally.—Wood tar resembles oil of turpentine in action but is not so powerful. As it contains creosote, phenol, oil of turpentine, etc., it is an antiseptic and a vascular stimulant. When rubbed in, it sometimes causes severe inflammation or pustules, of healthy sensitive skin, specially those parts which are hairy. It is a sedative to the nerves. Tar preparations, if used for any length of time, are apt to set up a very troublesome form of acne, called by Hebra, tar acne.

Internally.—It may cause indigestion, and in large doses symptoms of carbolic acid poisoning. It is absorbed and during elimination exerts a beneficial influence on the chronically inflamed bronchial mucous membrane, disinfecting, deodorising and checking profuse secretion, and promoting free expectoration. These effects may be obtained, according to Yeo, both when used as an inhalation or spray, and when taken internally.

Therapeutics

Externally.—Tar water is a stimulating lotion for wounds and sluggish ulcers. The ointment is an excellent application for chronic scaly skin diseases, such as psoriasis. Chronic eczema too is benefited by it.

Internally.—As an expectorant, wood tar only is used for chronic bronchitis, bronchiectasis and winter cough. It may be given in pills, capsules, or syrup. Apomorphine combined with syrup of tar and syrup of virginian prune makes an admirable cough linctus.

Non-official Coal-tar Preparations

1. **Chinosol.** *Syn.—Oxyquinoline Sulphate.*—Yellow minute crystalline powder, readily soluble in water. Used as a surgical antiseptic; 15 grains to the pint equals 1 in 40 of carbolic acid. Should not be used for the sterilisation of instruments, as it is apt to stain them badly.

2. **Dimol.**—A benzene derivative, Dimethyl-methoxyphenol, in combination with tri- and tetra-methylphenols. A powerful bactericide. 35 p.c. more efficient than phenol. A valuable intestinal antiseptic. *Dose.*—2 to 4 pulverettes after each meal.

BETANAPHTHOL

Betanaphthol. $C_{10}H_7OH$

Syn.—Beta-mono-hydroxy-naphthalene ; Naphthol.

Source.—Prepared by the fusion of sodium naphthalene-β-sulphonate with sodium hydroxide.

Characters.—White, crystalline lamellæ, or powder, with phenol-like odour, and pungent taste. *Solubility.*—1 in 1000 of *cold* water, 1 in 75 of *boiling* water, 1 in 2 of alcohol (90 p.c.), in olive oil, in glycerin.

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Incompatibles.—Camphor, ferric chloride, menthol, phenazone, and phenol.

B.P. Dose.—5 to 10 grs. or 0·3 to 0·6 grm.

Non-official Preparations

1. **Benzonaphthol.** *Syn.—Betanaphthol Benzoate.*—A white, tasteless, insoluble powder. Intestinal antiseptic and diuretic, splitting up into β-naphthol and benzoic acid in the intestines. In *dyspepsia* and *typhoid fever*. *Dose.*—5 to 15 grs. or 0·3 to 1 G.

2. **Betol.** *Syn.—Naphthalol; Betanaphthol Salicylate.*—A salicylate of β-naphthol-ester. In tasteless white crystals, insoluble in water. Splits up into salicylic acid and naphthol in the system. Used in *rheumatism* and *cystitis*. *Dose.*—5 to 10 grs. or 0·3 to 0·6 G.

Pharmacology and Therapeutics

Betanaphthol resembles carbolic acid in action but is not so corrosive. Naphthols irritate the mucous membrane, and when inhaled cause sneezing and coughing. They are excreted in the urine in combination with glycuronic and sulphuric acids, which give the urine a reddish-brown colour. During the course of excretion they cause pain in the bladder and urethra with strangury and swelling of the mucous membrane. It is a powerful antiseptic and disinfectant, both externally and internally. In scabies, ringworm, psoriasis and chronic eczema, the ointment (10 to 15 p.c.) having a less unpleasant odour may be used with success instead of tar, which it resembles in action. Internally it is chiefly used as a gastro-intestinal antiseptic in dyspepsia, pyloric obstruction, diarrhœa, and typhoid diarrhœa. It may be given in *cachets* or *pills*, or as an *emulsion* dissolved in oil. The pills may be coated with keratin.

Benzonaphthol is used as an intestinal antiseptic in combination with resorcin or bismuth salicylate, in putrefactive diarrhœa and diarrhœa of children.

In 15 gr. doses given every hour for three doses betanaphthol is a valuable remedy for ankylostomum duodenale and is preferable to thymol, being less irritating and cheaper. For method of treatment, *see* page 362. Both these drugs have however been replaced by oil of chenopodium and carbon tetrachloride.

The use of naphthols should be avoided in irritation of the bladder, kidneys and urethra.

SALOL

Salol. $C_{13}H_{10}O_3$ (Not official)

Syn.—Phenyl Salicylate.

Source.—By the interaction of salicylic acid and phenol.

Characters.—Colourless crystals, with a faint aromatic odour and slight taste. *Solubility.*—Almost insoluble in water, 1 in 15 of alcohol (90 p.c.), and in fixed and volatile oils.

Dose.—5 to 20 grs. or 0.3 to 1.2 grm.

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Pharmacology and Therapeutics

Internally.—It has no action on the stomach but splits up in the intestine by the fat-splitting ferment of the pancreatic juice into salicylic and carbolic acids which act as antiseptics and are then absorbed producing the usual effects. In large doses it is apt to cause *carboluria* and it should not, therefore, be given in too large doses, or for too long a period continuously, or to persons suffering from renal disease.

Its chief use is as an **intestinal** and **urinary antiseptic**, and it is given with advantage both *before* and *after* all operations upon the urinary tract. As an intestinal antiseptic it is falling into disrepute.

Coal-tar Dyes

These are classified as follows :—

1. Acridine Dyes : **Acriflavine, Proflavine, Rivanol** (*see* p. 491)
2. Azo Dyes : **Scarlet Red**
3. Triphenylamine Dyes : **Brilliant Green, Malachite Green, Gentian Violet**
4. Fluorescein Dyes : **Fluoresceinum Solubile, Mercurochrome** (*see* p. 448)
5. Phenolphthalein Dyes : **Iodophthaleinum**
6. Miscellaneous Dyes : **Methylene Blue, Indicarminum**

ACRIFLAVINA

Acriflavine. $C_{14}H_{14}N_3Cl,HCl$

Source.—Prepared by the combination of methyl-*p*-toluenesulphonate with 2 : 8-diacetyldiaminoacridine and subsequent hydrolysis of the product with hydrochloric acid.

Characters.—An orange-red or brownish-red, crystalline powder; no odour; taste, acid. *Soluble* in 3 parts of water, and in alcohol (90 p.c.). Almost insoluble in ether, in chloroform, in fixed and volatile oils, and in liquid paraffin.

Pharmacology and Therapeutics

Acriflavine is a powerful **antiseptic** and has the advantage over other antiseptics in that it is not a protoplasmic poison, on the contrary it becomes more active in the presence of serum, stimulates granulating process, and does not irritate tissues, nor interfere with phagocytosis. These derivatives therefore are the nearest approach to ideal antiseptics. It is twenty times more powerful than mercuric chloride, and about eight hundered times more so than carbolic acid. A solution of 1 in 100,000 inhibits *staphylococcus* and *B. coli* in an alkaline urine (*p*H 8.0), while it is effective only for *staphylococci* if the urine is acid (*p*H 6.0), but not *B. coli*. It is extensively used in modern surgical practice as a lotion, ointment or gauze, for sores, ulcers, abscess cavities, etc. The best method is to wash out with a solution (1 in 1000 of normal saline) and then to pack with gauze steeped in the solution. In combination with tannic acid it is used in the treatment of burns and scalds. A neutral solution, 1 in 4000 of saline, has been used as a bowel wash in ulcerative colitis, and as urethral irrigation (1 in 4000) in gonorrhœa. It is also useful in gonorrhœal infection of women. The method is to take a douche, and

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then lying down inject 25 c.c. of 1 in 1500 to 1 in 500 solution and retain for half an hour. This may be done twice a day. Similarly a solution of 1 in 1000 dropped into the eye and followed by wet dressing of strong solution of magnesium sulphate and sodium chloride is valuable in gonorrhœal ophthalmia, while a solution of 1 in 4000 is useful in conjunctivitis.

It is an urinary antiseptic, and a dose of 0.2 grm. (3 grs.) administered in capsules exerts an antiseptic action on urine against both the colon bacillus and the staphylococcus, but the urine must be alkaline. It however causes unpleasant symptoms of nausea and purging in a fair proportion of cases. It is of distinct value in acute infections of the urinary tract and has been used in the treatment of gonorrhœa in doses of $1\frac{1}{2}$ grs. (0.1 grm.) given by the mouth three times a day.

It has been given intravenously in pyelitis and rheumatism (2 to 5 c.c. of 2 p.c. solution), but the results have not been very encouraging. Good results have been obtained in epidemic encephalitis when neutral acriflavine solution (10 c.c. of 0.5 p.c.) is given intravenously. To avoid unpleasant by-effects the injections should be made slowly. Improvement is noticed after three injections, and after eight injections the improvement is marked.

The stains are removed by the application of a dilute solution of sulphurous acid.

METHYLTHIONINAE CHLORIDUM

Methylene Blue. $C_{16}H_{18}N_3ClS$

Source.—It is tetramethylthionine chloride. Prepared by the interaction of dymethyl-*p*-phenylene-diamine with thiosulphuric acid, and subsequent oxidation. Contains not less than 80 p.c. of methylene blue.

Characters.—A dark greenish, crystalline powder with a metallic lustre, or a dull, dark-green or brown powder. Almost odourless. *Soluble* in water, in alcohol (20 p.c.), and in chloroform.

B.P. Dose.—1 to 5 grs. or 0.06 to 0.3 grm.

Pharmacology and Therapeutics

Externally.—Methylene blue is an antiseptic. A 3 p.c. solution is useful in tropical ulcer and as a local application for eczema in children; after application it is allowed to dry and then covered with a thin layer of collodion. A lotion ($1\frac{1}{2}$ gr. to 1 pint) is useful as a bowel wash in dysentery. A solution, 1 in 1000 of normal saline, forms a valuable application in conjunctivitis, specially when due to *staphylococcus aureus*; and a 3 p.c. solution is applied to acute trachoma after the conjunctiva has been previously cocainised. A 5 p.c. aqueous solution applied as a paint twice daily is useful in erysipelas.

Internally.—Methylene blue is an antiseptic, analgesic

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and antiperiodic. As an analgesic it has been used in sciatica, migraine and neuralgia with doubtful results. Its use has been suggested in rheumatism, but is of little benefit except in cases of rheumatoid arthritis due to auto-intoxication from the alimentary canal. As an antiperiodic it has been used in malaria but is inferior to quinine and arsenic, although it may be usefully combined with them in $1\frac{1}{2}$ to 3 gr. doses.

Since it is excreted entirely by the kidneys it is used as a disinfectant to the urinary tract before and after operation on the kidneys and prostates, in pyelitis, gonorrhœa, cystitis and other septic conditions of the urinary tract. Combined with sandal wood oil it is valuable in staphylococcal infection of the bladder, while its therapeutic activity is enhanced by combining with hexamine (hexamine 3 grs. and methylene blue $\frac{1}{4}$ gr.), when it becomes equally active in acid and alkaline urine. It is recommended in renal and bladder tuberculosis, 0.1 grm. being the daily dose.

After its ingestion by the mouth it is found in large quantities in the bile, and is excreted in the urine colouring it bluish green. It has therefore been used to test the liver efficiency and the function of the kidneys. For the former 2 mgrms. is given before breakfast and the urine tested every 4 hours, for 12 hours. If the liver is deficient the urine will become green from 5th to 9th hour. For testing renal function, 5 ms. of a 10 p.c. solution is injected into the gluteal muscle and within 10 to 15 minutes blue jets of coloured urine should escape through the ureteral openings when observed under cystoscope. This test has been given up in favour of indigo carmine.

As it is eliminated by the gall bladder it has been used with some success in $\frac{1}{2}$ to $\frac{3}{4}$ gr. doses in cholangitis and cholecystitis.

The usual method of administration is in cachets or capsules. To prevent gastric or vesical irritation it may be combined with nutmeg. The solution for injection should be sterilised by heating in an autoclave or by tyndallisation.

Except slight vesical or gastro-intestinal irritation no untoward effects are observed with therapeutic doses, even after prolonged use. If it is rapidly absorbed in considerable amounts, symptoms of poisoning may appear showing signs of paralysis of the heart and respiratory centres.

INDICARMINUM

Indigo Carmine $C_{16}H_8O_8N_2S_2Na_2$

Syn.—Sodium indigotindisulphonate.

Source.—Prepared by the action of sulphuric acid on indigotin, neutralising it with sodium carbonate, and precipitating with sodium chloride.

Characters.—A blue powder, or blue granules with a coppery

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lustre. No odour; taste, saline. *Insoluble* in 100 parts of water, readily soluble in warm water. Precipitated by sodium chloride.

B.P. Dose.—$\frac{3}{4}$ to 1$\frac{1}{2}$ gr. or 0.05 to 0.1 grm. (subcutaneous or intramuscular injection); $\frac{1}{8}$ to $\frac{1}{4}$ gr. or 0.008 to 0.016 grm. (intravenous).

Action and Uses

It is used either intravenously, or by intramuscular injection to test the renal function and for diagnosis of surgical affections of the kidney. 4 to 10 c.c. of a 0.4 p.c. solution is usually given intramuscularly into the gluteal muscle. The colour should appear within 7 to 10 minutes, and the depth of the colouration gives a clue to the renal efficiency. It has also been used for the investigation of liver function. After intramuscular injection it is excreted by the healthy subject after 20 minutes and reaches maximum concentration within 2 to 3 hours. When the liver is diseased it is excreted earlier or later according to the nature of the affection of the organ. In diabetes it is earlier, in venous cirrhosis it takes a longer time. In pernicious anæmia it is delayed and the total quantity is less than usual. In cases of jaundice there is no excretion at all in the bile.

FLUORESCEINUM SOLUBILE

Soluble Fluorescein. $C_{20}H_{10}O_5Na_2$

Source—It is the disodium salt of fluorescein. Prepared by the condensation of resorcinol and phthalic anhydride. An orange-red powder; odourless; almost tasteless. *Soluble* in 1 part of water, and in 5 parts of alcohol (90 p.c).

Action And Uses

A 2 p.c. solution of fluorescein with 3 p.c. of bicarbonate of soda is used to diagnose corneal ulcers and abrasions. It does not stain the healthy tissue but produces a green stain when the dye penetrates any abrasion or ulcer on the eye. Similarly loss of substance in the conjunctiva produces a yellow stain. May be given by the mouth in 3 to 6 grm. doses, when it causes a yellow discoloration of the whole body which disappears in 24 hours; the normal eye is not coloured, but in intra-ocular disease, glaucoma or iritis, the aqueous humour is coloured green in about 20 minutes, while the conjunctiva remains unaffected. It is also used to test renal function.

Irradiated sodium fluorescein and other fluorescent salts have been used in the treatment of carcinomatous growths (Copeman, Coke and Gouldesbrough, *B. M. J.* 1929). A 2 to 2.5 p.c. solution of the sodium salt is painted over the affected area and part of the apparently healthy skin surrounding the growth, for two or three times, and then irradiated by X-ray or radium of moderate penetration. In deep-seated

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growths it is given internally or intravenously before irradiation. The dose *per os* is 2 gms. in capsules or cachets of 1 gm. each.

Non-official Coal-tar Dyes

1. **Proflavina.**—*Diamino acridine sulphate.*—In the form of orange-red or brown crystalline powder. Soluble 1 in 48 of alcohol (90 p.c.), 1 in 10 or less of glycerin, insoluble in liquid paraffin. *Uses.*—Similar to acriflavine but it is slightly hæmostatic.

2. **Gentian Violet.**—It is a mixture of the hydrochlorides of penta- and hexa-methyl-pararosaniline. Introduced as an antiseptic of great value for *gram-positive organisms.* Soluble in water but solutions cannot be made with normal saline as the dye is precipitated. Used for local action in *eczematoid dermatitis, folliculitis,* etc. The usual formula is gentian violet grs. 22; spirit rectified drs. 2; aqua ad 1 oz. Used intravenously in septicæmia, endocarditis, encephalitis, etc., but the results were not striking and dangerous reaction, like protein shock may appear. *Dose.*—0·003 to 0·007 grm. per kilo (=3 to 7 grs. for 10-stone man) intravenously in a 1/4 to 1 p.c. aqueous solution.

3. **Malachite Green.** *Syn.—Benzaldehyde Green.*—It is either the zinc double chloride or oxalate of Tetra-methyl-di-para-amino-Triphenyl-carbinol. A solution 1 in 2000 kills staphylococcus aureus in serum, and 1 in 5000 kills spores of B. subtilis. Much used as an *antiseptic wound dressing.*

4. **Briliant Green.**—*Tetra-ethyl-diamido-Triphenyl-carbinol.* In the form of either sulphate or zinc double chloride. Therapeutically the sulphate is used in golden yellow crystals. Soluble in water, normal saline, and alcohol, forming a green solution. 1 in 1000 solution is much used as a *painless antiseptic* dressing. Strongly *bactericidal.*

5. **Scarlet Red.**—$C_{21}H_{20}ON_4$—An azo-colouring matter of the secondary disazo group. Insoluble in water, more soluble in alcohol, and readily soluble in chloroform, oils and warm petroleum preparations. Promotes the growth of epithelium in the treatment of wounds, burns, and ulcers. Used as a dusting powder with boric acid, or as an ointment from 1 to 8 p.c.

4. Miscellaneous Compounds

LIQUOR FORMALDEHYDI

Solution of Formaldehyde. CH_2O

Syn.—Formalin; Formol.

Source.—An aqueous solution of formaldehyde, with a variable amount of ethyl alcohol or methyl alcohol, or both. Contains 37 to 41 p.c. w/v of CH_2O.

Characters.—A colourless liquid with a characteristic pungent odour. Freely soluble in water, and in alcohol (90 p.c.).

Dispensing hints.—It should be kept in well-stoppered bottles, in a moderately warm place.

Non-official Preparations

1. **Amyloform.**—By the action of formaldehyde on starch. An inodorous, insoluble, white powder, unaltered by heat. Used as an *antiseptic dressing for wounds.*

2. **Paraformaldehydum, U.S.P.**—A polymer of formaldehyde, in white friable amorphous masses, slightly soluble in water, more readily soluble in hot water with formation of formaldehyde. Heated in an enclosed spirit-lamp, it sublimes, unites with the products of combustion, and is converted into formaldehyde. Has been recommended as a *disinfectant for the sick-room* after illness.

Pharmacology and Therapeutics

Formalin is a caustic. When diluted with ten times its bulk of water it is useful as a hardening histological agent or

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as a preservative for museum specimens. The solution is a powerful germicide and in dilutions of 1 in 200 kills most micro-organisms, it possibly acts by combining with some amino group in the protein molecule. Being a powerful antiseptic, it is used for sterilising instruments, and for preservation of corpses for dissection, but on account of its necrotic action on the skin it is not suitable for treatment of wounds. It causes soft corns to shrivel up.

A solution of 1 in 500 may be used as an antiseptic gargle or mouth-wash in stomatitis, a 1 p.c. solution of the liquor is useful as a spray in diphtheria and whooping cough. A 30 p.c. solution in glycerin makes an excellent pigment in ringworm and parasitic skin diseases. Applied to sarcomata and bleeding tumours, it hardens their substances and facilitates their removal. It also lessens the fetid smell in bromidrosis of the feet.

Formaldehyde 1 part, chloroform 1 part, and alcohol 2 parts, is recommended as an antiseptic inhalation in phthisis; 5 to 10 drops being sprinkled on cotton-wool, or inhaled from the pad of an oro-nasal inhaler.

It may be used as a spray to disinfect infected rooms, or may be used as a gaseous disinfectant either by using paraform tablets or by generating the gas by adding pot. permanganas to the solution. *Paraform* requires a special apparatus, which is known as "Formogene" or "Alformant" lamp. The vapour thus produced disinfects surface only; it does not penetrate or disinfect fabrics.

Formaldehyde solution is **incompatible** with ammonia and all oxidising substances and renders gelatin insoluble.

ACETONUM

Acetone. Dimethyl ketone. C_3H_6O

Source and characters.—Obtained by the dry distillation of calcium acetate. A colourless, transparent, mobile and volatile liquid. Odour, characteristic; taste, pungent and sweetish.

Dose.—60 to 90 ms. or 4 to 6 mils.

Action and Uses

Acetone is a solvent for resin, fat, cantharidin, etc. Its action is similar to that of ethylic alcohol. A solution of iodine in acetone (1 in 50) is used to sterilise catgut. It has been used in asthma as an expectorant and antispasmodic, and as an antiseptic (with equal parts of alcohol) for sterilising the hands and site of operation.

ACIDUM BORICUM

Boric Acid. H_3BO_3

Syn.—Boracic Acid.

Source.—Obtained by the interaction of sulphuric acid and native borates. Contains not less than 99.5 p.c. of orthoboric acid.

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Characters.—White crystals, or powder; unctuous to touch. Odourless. Taste, slightly acid and bitter. *Solubility.*—1 in 25 of water, 1 in 4 of glycerin, 1 in 30 of alcohol (90 p.c.).

Incompatibles.—Sodium salicylate in powder forming boro-salicylate.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Official Preparations

1. **Glycerinum Acidi Borici.** *Syn.—Glycerite of Boroglycerin.*—31 p.c. A substitute for Boro-glyceride. **B.P. Dose.—10 to 30 ms. or 0.6 to 2 mils.**
2. **Unguentum Acidi Borici.**—10 p.c.

Non-official Preparation

1. **Pigmentum Acidi Borici.** *Syn.—Solutio Saturans.*—Boric Acid 1, Ether 3, Alcohol (90 p.c.) 6. Used in *ringworm*, etc.

BORAX

Borax. $Na_2B_4O_7,10H_2O$

Syn.—Borax Purificatus; Biborate of Sodium; Sodii Boras.

Syn. I.V.—*Shohaga.* Beng., Hind.

Source.—Obtained from native borax, or by boiling native calcium borate with solution of sodium carbonate. Contains not less then 99 to 103 p.c. of sodium borate.

Characters.—Transparent, colourless, odourless, efflorescent crystals, with a weak alkaline reaction. Taste, saline, alkaline. *Solubility.*—1 in 25 of water, 1 in 1 of glycerin, insoluble in alcohol (90 p.c.). It gives a yellow colour to the flame.

Incompatibles.—Mineral acids, most metallic salts, mucilage of acacia, also alkaloidal salts, *e.g.*, cocaine hydrochloride.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Official Preparations

1. **Glycerinum Boracis.**—12 p.c. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**
2. **Mel Boracis.** *Syn.—Borax Honey.*—10 p.c.

Non-official Preparations

1. **Nebula Alkalina Co., B.P.C.** *Syn.—Compound Alkaline Spray.*—Sod. bicarbonas 15 grms., borax 15 grms., phenol 7.5 grms., glycerin 250 mils, water to 1000 mils. As a spray or irrigation in *catarrh of the nose and throat.*

2. **Pulvis Sodii Chloridi Co.**—Sodium chloride 4; sodium bicarbonate 4; sucrose 4; borax 4. A saltspoonful in half a tumblerful of warm water as a gargle. Useful in *inflamed throat.*

Pharmacology of Boric Acid and Borax

Externally.—Both boric acid and borax are non-irritating and mild antiseptics. In 2½ p.c. solution almost all forms of bacilli stop growing, but they are not destroyed. They kill micro-organisms, but their action is entirely local. Some skins, however, are very sensitive to the action of boric acid, which is apt to produce a troublesome herpes in such cases.

Internally. **Gastro-intestinal tract.**—Taken by the mouth in large doses they cause gastro-intestinal irritation, evidenced by vomiting and purging. Both borax and boric acid are rapidly absorbed by the bowel, and do not affect the intestinal putrefaction.

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Urinary tract.—Boric acid and borax are rapidly excreted in the urine, causing increase in the elimination of both water and urea. But the elimination becomes slow after twelve hours so that boric acid is inclined to be cumulative. Borax, like any other alkaline preparation, renders the urine alkaline. They are good genito-urinary antiseptics and differ from other more active drugs in retaining their disinfectant action when the urine is alkaline. The administration of a few doses often has a marvellous effect in rendering a foul alkaline urine perfectly clean and sweet. Repeated small doses have induced albuminuria especially in persons predisposed to it. Maximum daily dose should not exceed 1 dr.

Toxic action.—Boric acid was used as a food preservative, but owing to cases of poisoning its use has been prohibited. The symptoms are loss of appetite, mild gastro-enteritis, muscular weakness, albuminuria and prostration. The prolonged use, either internally or externally, has led to falling of the hair, eczema and psoriasis. Œdema and swelling of the skin may appear, and a gray line on the gums, similar to that seen in lead poisoning, is stated to occur along with irritation of the mouth. Also bullous, cutaneous lesions or a dermatitis. Renal disease seems to increase the susceptibility to poisoning.

Therapeutics of Boric Acid and Borax

Externally.—Being a non-irritant, it is largely employed in surgical dressings. The ointment is applied to wounds, ulcers and burns. As its action is entirely local its use is of no value in deep suppurating cavities. It is used as an eye-wash in ophthalmia, and as an injection in leucorrhœa, gonorrhœa, ozæna (10 grs. to 1 oz.), and otorrhœa. In cystitis, the irrigation of boric acid (1 in 100) is a capital local application. Pityriasis of the body and scalp, eczema of the ear and scalp, and cracked nipples are benefited by boric acid applications. Borax (1 dr. to water 4 ozs.) removes prurigo of the labia and anus. The wearing of socks soaked in warm saturated solution of borax removes the smell of fetid perspiration of the feet.

Internally.—Borax is used as a gargle in mercurial salivation and aphthous sores of the mouth. Borax tablets slowly dissolved in the mouth reduce hoarseness. Borated tincture of myrrh is a valuble local paint for ulcerated gums. Glycerin boracis 1 dr., tincture of myrrh 10 ms. and water to 1 oz., make a good all-round mouth-wash. Mel boracis is a soothing and antiseptic application to inflamed mucous membrane and is specially useful in thrush. Borax is an excellent remedy for disinfecting foul urine. To clear putrid ammoniacal urine, boric acid is superior to borax; three or four 15 gr. doses rendering it quite clear. Borax has been

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used to increase labour pains, and with bromides in epilepsy, but it is doubtful if it does any good.

Prescribing hints.—The powder may be given in cachets or solution. Borax being alkaline should not be combined with cocaine or other alkaloids. Combined with acetate of lead or sulphate of zinc insoluble borates are precipitated. Being alkaline it liberates chloroform when prescribed with chloral hydrate.

OLEUM HYDNOCARPI

Hydnocarpus Oil

Source.—A fatty oil obtained by cold expression from the fresh, ripe seeds of *Hydnocarpus Wightiana*.

Characters.—A yellowish, or brownish-yellow oil, or soft cream-coloured fat, with a characteristic odour and somewhat acrid taste. Partially *insoluble* in cold alcohol (90 p.c.), freely *soluble* in hot alcohol; miscible with ether, chloroform and carbon disulphide.

Composition.—Same as chaulmoogra oil.

B.P. Dose.—0.3 to 1 mil, increasing to 4 mils; or 5 to 15 ms. increasing to 60 ms. For subcutaneous and intramuscular injection, 2 mils, increasing to 5 mils; or 30 ms. increasing to 75 ms.

OLEUM HYDNOCARPI AETHYLICUM

Ethyl Esters of Hydnocarpus Oil

Source.—It consists mainly of ethyl esters of chaulmoogric and hydnocarpic acids, and is produced by esterifying the fatty acids of hydnocarpus oil and ethyl alcohol, with industrial methylated spirit, the crude product being washed with sodium carbonate solution to remove fatty acids, and purified by distillation.

Characters.—A colourless, or faintly yellow, limpid oil, with a characteristic odour and slightly acrid taste. *Soluble* in less than 6 volumes of cold alcohol (90 p.c.), miscible with ether, chloroform, and carbon disulphide.

B.P. Dose.—Same as hydnocarpus oil.

OLEUM CHAULMOOGRAE

Chaulmoogra Oil. (*Not official*)

Syn.—Gynocardia Oil. **Syn. I.V.**—*Chalmugra tel*, Beng., Hind.

Source.—The fatty oil expressed from the seeds of *Taraktogenos Kurzii*.

Characters.—Brownish-yellow oil of varying consistence. Odour, characteristic. Taste, acrid. Liquefies at 22° to 30°C. *Solubility.*—Partly in alcohol (90 p.c.), freely in ether, chloroform, and carbon disulphide.

Composition.—(1) Glycerides of *Chaulmoogric acid*, $C_{18}H_{32}O_2$. (2) Glycerides of *Palmitic acid* and Fatty acids. (3) *Hydnocarpic acid*.

Dose.—5 to 10 ms. or 0.3 to 0.6 mil gradually increased to 30 to 60 ms. or 2 to 4 mils.

Non-official Preparations

1. **Sodii Chaulmoogras.** *Syn.*—*Sodium Gynocardate.*—Two forms are prepared.

(*a*) **Sodii Chaulmoogras** "A" (Martindale) comprises the salts of higher fatty acids with relatively high melting point, and

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(*b*) **Sodii Chaulmoogras "C"** (free from palmitate—Martindale) contains the lower homologues with combined melting point 25°C. approximately. Have been used intravenously in 2 to 3 p.c. solution in *leprosy*. *Dose.*—1 to 3 grs. in pills, tablets or injections.

2. **Æthylis Chaulmoogras, U.S.P.** *Syn.—Ethyl Chaulmoograte*; *Moogrol.*—The ethyl esters of the fatty acids of chaulmoogra oil. A clear, pale-yellow liquid, having a slight fruity odour. Insoluble in water, but miscible with alcohol, chloroform and ether. *Dose, U.S.P.*—By mouth or by intramuscular injection, 1 c.c. or 15 ms.

3. **Sodii Hydnocarpus.** *Syn.—Alepol.*—Sodium salt obtained from the low melting fraction of *Hydnocarpus Wightiana Oil*. A 3 p.c. solution is given intramuscularly or subcutaneously under the skin lesions twice weekly. *Dose.*—0.5 c.c. (of 3 p.c. solution) increased to 5 c.c. or more.

Pharmacology of Hydnocarpus and Chaulmoogra Oils

Externally.—Chaulmoogra oil when rubbed into the skin stimulates the local circulation and the local nerves. If rubbed too long or every day for some time, it is a **rubefacient.**

Internally.—Chaulmoogra oil has been used in the treatment of leprosy from time immemorial, but the precise nature of its action is still a matter of dispute. One school holds that these acids of chaulmoogra and hydoncarpus oils have no lethal effect on the leprosy bacillus, and it has been suggested that they act by producing a reaction with fever whereby lepra cells are ruptured and liberate the bacilli which act as antigens and increase the immunity response. The other school maintains that they increase the blood lipase which dissolves the waxy or fatty coat of the bacilli thus making them favourable for the oils to act on. It is said that in this action the large mononuclear leucocytes, which increase after an injection, assist in the transport of the oil throughout the body. Yet others (Walker and Sweeney) believe that these oils, because of the presence of unsaturated fatty acids, possess a special bactericidal effect on acid fast bacilli which is the underlying cause of the specificity of these oils.

Read* found that in toxic doses the hydnocarpates produce hæmolysis of the red blood-corpuscles, renal irritation with hæmoglobinuria, anorexia, nausea and vomiting. These effects are not observed in therapeutic doses. Other effects following their use are:—

Immediate effects.—Dizziness, choking sensation and pain in the chest. Sometimes dimness or temporary loss of vision. The cause of these reactions is not known.

Local effects.—Induration, pain and abscess formation, more common after subcutaneous injections than after intramuscular injections. Regional lymph glands sometimes become enlarged or even ulcerated.

General symptoms.—Headache, malaise, fever, insomnia, anorexia, abdominal pain and a sensation of general heat.

* Journal of Pharmacology and Experimental Therapeutics, XXIV. 1924

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Albumin and casts, or even nephritis may appear. The so-called leprous reaction consists of fever, cutaneous eruption, neuritis, arthritis, orchitis and inflammatory reactions of the eye (iritis or iridocyclitis).

Therapeutics of Hydnocarpus and Chaulmoogra Oils

Formerly these oils were used by the mouth, but prolonged use in large doses upsets the stomach and therefore the ethyl esters of hydnocarpic and chaulmoogric acids are now used either intramuscularly or intravenously. The sodium salts and esters of these acids being less irritating are injected intramuscularly or intravenously. Muir recommends the following E. C. C. O. mixture as effective, convenient, and painless when given intramuscularly. It consists of ethyl esters of fatty acids of hydnocarpus oil 1 c.c., creosote (double distilled) 1 c.c., camphor 1 grm. and olive oil $2\frac{1}{2}$ c.c. Of this 0.25 c.c. is given twice a week, and gradually worked up to 2 to 5 c.c. by increases of 0.25 c.c. with each injection as long as no marked febrile or local reaction occurs. With this treatment the nodules become soft, disintegrated and eventually are absorbed, while in early cases all clinical signs disappear after treatment extending over six months.

Prescribing hints.—The oral method is not so popular now. The subcutaneous injection into the diseased patches should be the method of choice. The area of the diseased skin is chosen and the needle is pushed into the subcutaneous tissue and a fraction of the mixture is injected, withdraw the needle partially and reinsert it at a different angle and inject a little more, and in this way with one insertion of the needle the drug is injected at different angles. Always inject into the loose subcutaneous tissue and not into the skin as this may cause sloughing. When large doses are required, intramuscular injections are given into the upper half of the gluteal region, care being taken to avoid the region of the sciatic nerve. Before pushing the piston home be sure that the needle has not entered a vein.

Class D: Parasiticides

Parasiticides are divided according to their action on the different varieties of parasites as follows:—

1. Tinea and its varieties: **Mercury** (*see* p. 444), **Iodine** (*see* p. 527), **Phenol** (*see* p. 532), **Salicylic Acid** (*see* p. 413), **Boric Acid** (*see* p. 546), **Thymol** (*see* p. 519), **Formalin** (*see* p. 545), **Chrysarobin**

3. Scabies or itch: **Sulphur, Ichthammol, Storax** (*see* p. 498), **Balsam of Peru** (*see* p. 499), **Sandal Wood Oil** (*see* p. 388)

4. Pediculi or lice: **Mercury** (*see* p. 444)

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CHRYSAROBINUM

Chrysarobin

Source.—A mixture of substances obtained from araroba, by extracting with hot benzene, evaporating to dryness and powdering.

Characters.—A light, microcrystalline, yellow, tasteless, inodorous powder. *Solubility.*—Entirely in hot chloroform and in hot benzene, slightly in alcohol (90 p.c.), almost insoluble in water.

Composition.—(1) *Chrysarobin* or *Chrysophanolanthranol.* (2) *Chrysophanic Acid.*

Official Preparation

1. **Unguentum Chrysarobini.**—1 in 25.

Non-official Preparations

1. **Pigmentum Chrysarobini.**—Chrysarobin 1, Gutta-percha Solution 9. Dissolve. Does not stain cloth.
2. **Unguentum Acidi Chrysophanici** (Malcolm Morris).—Acid Chrysophanic 20 grs., Paraffin Liquid 2 drs., Lanolin to 1 oz.

Pharmacology

Externally.—Chrysarobin is a powerful irritant to the skin producing a sort of erythematous inflammation. It does not irritate so much the diseased parts as the healthy skin. It destroys low vegetable growths infesting the surface of the body, and is therefore a powerful parasiticide. It is absorbed from the skin.

Internally.—Even in small doses, $\frac{1}{8}$ gr., it powerfully irritates the gastro-intestinal mucous membrane, causing anorexia, vomiting and purging with gripes. It is therefore a powerful gastro-intestinal irritant.

It is eliminated chiefly by the kidneys and partly by the skin. The urine is stained purple.

Therapeutics

Externally.—As a *parasiticide* it is a valuable remedy for ringworm and other forms of tinea. The B.P. ointment or the pigment are suitable preparations. It is also useful in many chronic dry skin diseases such as psoriasis, eczema, and acne rosacea. An ointment ($\frac{1}{2}$ to 1 dr. in 1 oz. of heated soft paraffin) rubbed into the parts night and morning, acts like a charm in chronic psoriasis. Applied thus locally it also acts constitutionally, probably by absorption, since after a time patches of psoriasis to which it has never been applied also show signs of improvement and tend to disappear.

Internally.—It should not be prescribed internally on account of its irritating properties, though success has sometimes attended its internal administration in psoriasis, eczema, acne, etc.

Prescribing hints.—Chrysarobin should not be applied to the face as it is apt to cause conjunctivitis, though a mild

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ointment (15 grs. to 1 oz.) may not produce much irritation if applied to the scalp. To prevent the irritation of the surrounding healthy skin its application should *be exclusively confined to diseased islands.* This may best be done by painting the parts with pig. chrysarobini and covering the pigment with collodion, or by applying a stiff ointment covered over with a piece of isinglass or Mead's plaster. The stains on the linen may be removed by a weak solution of potash or chlorinated lime, and partially by vegetable acids. Chrysarobin should never be applied to a large surface of the body at one time, otherwise it may produce most unpleasant symptoms. In cases of extensive ringworm, treat the disease bit by bit, curing one patch before attacking another.

SULPHUR SUBLIMATUM

Sublimed Sulphur

Syn.—Flowers of Sulphur.

Source.—Obtained from native sulphur, or from sulphides.

Characters.—A fine, yellow, slightly gritty powder; odourless; tasteless. Burns with a blue flame forming sulphur dioxide. *Almost insoluble* in water, in alcohol (90 p.c.), incompletely soluble in carbon disulphide.

B.P. Dose.—15 to 60 grs. or 1 to 4 grm.

Enters into.—Pulv. glycyrrhizæ co.

Official Preparation

1. **Unguentum Sulphuris.**—10 p.c.

Non-official Preparations

1. **Confectio Guaiaci Co.**, L.H. *Syn.—Chelsea Pensioner.*—Guaiacum 2, sublimed sulphur 4, mustard 4, nitrate of potash 1, rhubarb 1, honey or treacle to 64. *Dose.*—1 to 2 drs. or 4 to 8 G.
2. **Unguentum Sulphuris Co.**, B.P.C. *Syn.—Wilkinson's Ointment.*—Soft soap 30, sublimed sulphur 15, precipitated chalk 10, tar 15, lard 30.

SULPHUR PRAECIPITATUM

Precipitated Sulphur

Syn.—Milk of Sulphur.

Source.—Obtained by adding hydrochloric acid to a solution prepared by boiling sulphur and lime with water.

Characters.—A pale greyish-yellow or pale greenish-yellow, soft powder, free from grittiness; tasteless and free from odour of hydrogen sulphide. Burns with a blue flame forming sulphur dioxide. Almost insoluble in water, in alcohol (90 p.c.); almost completely soluble in carbon disulphide.

B.P. Dose.—15 to 60 grs. or 1 to 4 grm.

Official Preparation

1. **Confectio Sulphuris.**—45 p.c. sulphur. **B.P. Dose.—60 to 120 grs. or 4 to 8 grm.**

Non-official Preparations

1. **Trochiscus Sulphuris.** *Syn.—Garrod's Lozenges.*—5 grs. in each.
2. **Contramine.** *Syn.—Diethyl-ammonium diethyl-dithiocarbamate.*—Useful in

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syphilis, arthritis, fibrositis, skin affections and *chronic ulcers.* Prevents and ameliorates metallic poisons of various kinds. *Dose.*– 0.05 to 0.25 grm. (¾ to 4 grs.) in 1.5 to 3 c.c. of cold sterile water or saline, intramuscularly. Must not be heated. Intravenously, 0.25 grm. in 10 c.c. saline containing 1 grm. of glucose.

Pharmacology of Sulphur

Externally.—When applied to the whole skin pure sulphur has no effect, but if it be mixed with any greasy substance (sebaceous secretion), some of it is converted into sulphide which acts as a mild irritant, causing dilatation of vessels and in delicate skins, sometimes even severe dermatitis. Sulphide being a parasiticide, sulphur rapidly causes death of the itch insect when applied locally. When it is brought into contact with open wound, more sulphide is formed which causes more severe irritation to raw surfaces, and sometimes destruction of tissues.

Internally. **Gastro-intestinal tract.**—Being insoluble in the fluids of the mouth, sulphur has no taste, neither does it undergo any change in the stomach. When however it reaches the small intestine, it comes in contact with the alkaline bile, and a small portion being converted into an alkaline sulphide, is absorbed as such, but the greater portion passes unchanged through the bowels and is excreted with the fæces. The amount absorbed depends upon the preparation used and Buchheim has shown that as much as 46 p.c. of the finely divided precipitated sulphur can be detected in the urine, but only 15 p.c. of sublimed sulphur is eliminated in this way. In the intestine sulphur acts as a mild **laxative,** causing soft motions without any colic due to sulphides which act as mild stimulants to peristalsis. Some sulphuretted hydrogen is generated in the bowels which also stimulates peristalsis, but this gas forms the chief objection to its use, as the smell is very offensive.

Remote effects.—It is absorbed into the blood as sulphides and sulphuretted hydrogen which is a powerful poison, first reducing and then decomposing hæmoglobin, giving rise to marked cyanosis with coma and muscular weakness. But sulphur is never used in sufficiently large doses to produce these remote effects, but it is probable that many of the obscure nervous symptoms that accompany certain forms of dyspepsia and constipation, are due to the development of sulphuretted hydrogen gas in the bowel and its subsequent absorption into the blood.

Excretion.—Sulphur is excreted chiefly as sulphates by the urine, and as sulphuretted hydrogen by the lungs, sweat and milk. It gives an offensive smell to the breath, and blackens silver ornaments worn next the skin.

Therapeutics of Sulphur

Externally.—Sulphur is largely used to disinfect infected

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rooms. For this purpose about a pound of sulphur is broken and moistened with methylated spirit and allowed to burn in a vessel. The active agent is SO_2 gas, which by acting as a reducing agent acts as a powerful disinfectant. About two pounds when burnt will give off over 2 p.c. of gas to the atmosphere of the room and will disinfect a room of 1000 cubic feet.

It is chiefly used in the treatment of **scabies** and **itch**. If thoroughly applied it is certain in its effects and provided the strength is properly adjusted to the condition of the patient's skin no undue irritation is caused. The gritty sublimed sulphur is better as it mechanically opens up the burrows and brings the drug into closer contact with the acarus, the eggs and embryos of which lie beneath the superficial layers of the epidermis. On account of the irritation and disagreeable smell some use storax or balsam of Peru in the treatment of this disease.

If scabies be complicated by eczema and impetigo, the best preparation to use is Unguentum Sulphuris Co., B.P.C. This ointment accompanied by the use of warm bath, is applied twice daily, and cures in three days.

For the cure of **acne**, a lotion consisting of sulphur 1 dr., glycerin 1 oz. in 10 oz. of rose water should be substituted for the ointment which is a very unsightly application to the face. Great relief is often obtained in rheumatism and sciatica by rubbing the affected limbs with sulphur and then applying flannel bandages.

Internally.—Sulphur is largely used as a laxative, and as it causes soft motions without any pain it is specially used in hæmorrhoids and fissures of the anus, in which case it not only acts as a purgative, but it has also a direct soothing effect on the hæmorrhoidal vessels. Equal parts of the confections of senna and sulphur is a favourite prescription. Too long use of this drug leads to dyspepsia and catarrh of the bowels. It is given in plumbism to prevent reabsorption of lead from the intestines. In the form of *Chelsea Pensioner* it is a favourite remedy in chronic rheumatism and gout. It is used in many chronic skin diseases, as psoriasis, impetigo, eczema and acne, but it is doubtful whether it does any good. Sulphur dissolved in olive oil and given intramuscularly has been recommended in arthritis deformans and chronic rheumatic polyarthritis.

POTASSA SULPHURATA

Sulphurated Potash

Syn.—Liver of Sulphur.

Source.—It is a mixture of salts of potassium, chiefly sulphides. Obtained by heating together sublimed sulphur 500 gms. and carbonate of potash 1000 gms. Contains 43.5 p.c. of total sulphur.

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Characters.—Solid fragments, externally greenish-yellow, internally pale liver-brown, rapidly changing to greenish-yellow on exposure to air; odour of hydrogen sulphide. Taste, alkaline, acrid. *Soluble* in water.

Non-official Preparation

1. **Calx Sulphurata.**—A greyish-white powder with a smell of hydrogen sulphide. *Dose.*—1/4 to 1 gr. or 0.015 to 0.06 grm.

Pharmacology of Alkaline Sulphides

Externally.—Both sulphurated lime and sulphurated potash are irritants and parasiticides. Sulphides, specially of calcium and barium are valuable depilatories.

Internally.—The alkaline sulphides are easily decomposed in the stomach into sulphuretted hydrogen to which they owe their virtues. In the stomach they act as local irritants, and in the intestine stimulate peristalsis and act as purgatives. The gas however gives rise to disagreeable eructations. In small doses they merely cause a sensation of warmth in the epigastrium and determine gentle relaxation of the bowels.

The sulphides added to drawn blood reduce oxyhæmoglobin, making the blood dark venous colour, and at the same time form a combination with hæmoglobin. This compound is not formed in the blood of the living animal.

Therapeutics of Alkaline Sulphides

Externally.—Unguentum Potassæ Sulphuratæ, B.P.C. (1 in 80 with hard and soft paraffin) may be used as a substitute for sulphur ointment in the treatment of scabies, but a better preparation is Lotio Calcis Sulphuratæ or Vleminckx' solution (slaked lime 4, sublimed sulphur 4, water to 20, boil till sulphur is dissolved), which will cure the disease in half an hour.

In the form of a bath (4 oz. to 30 gals. of water) sulphurated potash is used in chronic rheumatic arthritis and myalgia, chronic nervous diseases, and in chronic metallic poisoning. Sulphide baths with the internal administration of mercury constitute the celebrated Aix treatment for syphilis.

Internally.—The natural sulphurous waters are specially useful in follicular pharyngitis and are much resorted to by public singers in Europe. Sulphides are used to arrest and prevent suppuration, specially in the treatment of boils, carbuncles and scrofulous glands.

ICHTHAMMOL

Ichthammol

Syn.—Ammonium Ichthosulphonate. Ichthyol.

Source.—Consists of the ammonium salts of the sulphonic acids of an oily substance, prepared from a bituminous schist, together with ammonium sulphate and water. Contains not less than 10.5 p.c. w/w of organically combined sulphur.

Characters.—An almost black, viscid liquid. *Soluble* in water, partly in alcohol (90 p.c.), miscible with glycerin and with fixed oils.

B.P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm

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Non-official Preparations

1. **Ichthammol Collodion.**—1 in 8 of collodion. For *eczema* and *erysipelas.*
2. **Pasta Ichthammol.**—Ichthammol 10, gelatin 10, glycerin 60, water 25. Dries quickly and is easily washed off.
3. **Ichthalbin.** *Syn.—Ichthosulphol Proteinate.*—A tasteless, odourless brown powder. A combination of ichthammol and albumen. In eczema and nervous intestinal affections. *Dose.*—¾ to 15 grs. or 0.05 to 1 grm.

Pharmacology and Therapeutics

Ichthammol contains a high percentage of sulphur, and possesses antiseptic and antiparasitic properties. As an antiseptic it is less powerful than phenol. It is a mild astringent to mucous surface and exposed tissue. Diluted with glycerin (1 in 8) it is extensively used as an emollient and demulcent application. An ointment (5 p.c. with lanoline), alone or combined with zinc oxide forms an excellent application in obstinate cases of ulcerative blepharitis; and a 30 p.c. ointment is used for wounds and burns of the first degree. A stronger ointment gives good results in erysipelas. It forms a valuable application in mumps and various skin diseases. To aid absorption of inflammatory products it is used in gynæcological practice as tampons with glycerin (5, 10 or 20 p.c.).

In conjunction with conium (page 240) it forms a valuable application in hæmorrhoids, either in the form of a suppository (3 grs. in each) or as an ointment.

It has been used internally as an intestinal antiseptic, and in rheumatism and other skin affections.

GROUP XX

NUTRIENTS

Vitamins, Irradiated Ergosterol, Yeast, Cod-liver Oil, Sucrose, Lactose, Glucose, Dextrose, Lævulose, Gelatin, Lecithin

VITAMINS

Observations made by Funk and others show that in addition to the different proximate principles, there are certain accessory materials that are necessary either because they play an important role in the synthesis of the body, or influence in some indirect way the normal direction and character of the metabolism. It has been shown that polyneuritis is caused by a diet exclusively of polished rice, *i.e.*, rice from which the outer layers of the grain have been removed. If however the polishings are restored to the diet, the condition disappears. It is believed that the polishings contain some material essential to the body metabolism. They are as a rule present in raw food and are deficient in cooked food. Certain foods manage to retain their vitamins to some extent even after cooking.

These accessory substances are essential to the normal growth and health. The part they play in the metabolism is not clearly understood and since very minute quantities are required for the maintenance of health, it has been suggested that they stimulate the production of hormones and are not directly concerned in the nutrition of body cells or the general growth of the organism.

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Vitamins exist in the foods in very minute quantities, and a vitamin free diet gives rise to certain diseases, generally known as deficiency diseases, and may even cause death. Rickets, pellagra, scurvy, beriberi, xerophthalmia or keratomalacia, osteomalacia are some of the diseases caused by the lack of vitamins in the food. Green vegetables and fruits are rich in vitamins, and both man and animals obtain their vitamins from these sources. Vitamins are produced only in plants from which they pass directly with vegetable foods, and indirectly with animal foods, into the system.

Drummond has shown that the whole fat-soluble vitamins are contained in the 1 p.c. of the non-saponifiable matter in cod-liver oil. Half of this active residue is cholesterol and is inactive. Fractional distillation of the remainder under low pressure shows that the whole of the active portion is contained in the fraction boiling between 180° to 200° C. This active fraction consists very largely of an unsaturated alcohol, and contains only the elements carbon, hydrogen and oxygen.

Vitamins have been classified into :—

(*a*) Growth Promoting Vitamin, or *Fat-soluble A*
(*b*) Antineuritic Vitamin, or *Water-soluble* B_1
(*c*) Antiscorbutic Vitamin, or *Water-soluble C*
(*d*) Antirachitic Vitamin, or *Fat-soluble D*
(*e*) Anti-sterility Vitamin, or *Fat-soluble E*
(*f*) Pellagra Preventive Vitamin, or *Vitamin* B_2 or *G*.

(*a*) *Growth Promoting Vitamin, or Fat-soluble A.*—The deficiency of this vitamin retards growth and lowers resistance, either local or general, to bacterial infection, causes xerophthalmia or inflammation of the eye and night blindness, and increases susceptibility to various lung, skin and other infections. Its absence also causes paralysis of various types from demyelination of the spinal cord ; and Mellanby has suggested that the paralysis associated with famine, e.g. convulsive ergotism, may be the result of the absence of this vitamin. Mellanby has further shown that its deficiency causes pyorrhœa alveolaris in dogs. It has however been shown recently that the deficieny of this vitamin does not appreciably lower the incidence of common cold and related catarrhal conditions, nor does it modify in any apparent manner the outcome or course of pneumonia, and there is reason to doubt its value in lessening the risk of sepsis and other complications in child-birth (Drummond). Any effect which may follow its use is possibly indirect, due to general improvement of health and vigour. Its relation to the formation of urinary calculi was studied by McCarrison, who observed that a deficiency of this vitamin and of phosphates in the diet together with the presence of excess of calcium and some unknown toxic substances found in certain cereals encouraged the formation of stones so common in certain parts of India.

Vitamin A is closely related to *carotene* which is converted into it in the body. In fact it is considered as the degradation product of the plant pigment carotene produced in the liver from lipochrome. It is however interesting to note that cod-liver oil, though rich in this vitamin, contains none of this pigment. Pure carotene has been adopted as the standard of vitamin A activity ; 0.001 mgrm. being designated as vitamin A unit.

The main sources of this vitamin are (*a*) certain fats of animal or vegetable origin ; (*b*) chlorophyll in green vegetables. It is preserved in these vegetables even when dried. It is found in abundance in cream, butter, beef fat, cod-liver oil, halibut liver oil and other fish oils, mammalian liver and yolk of eggs. Milk does not lose this vitamin by boiling or pasteurising, but when evaporated by vacuum or aeration methods it is destroyed. Vegetable oils contain very little vitamin A.

(*b*) *Antineuritic Vitamin, or Vitamin B Complex.*—Vitamin B is now

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considered to contain six separate entities of which the important ones are antineuritic vitamin (B_1) and pellagra preventive vitamin (B_2 or G). Crystalline vitamin B_1 has been isolated in the form of *torulin* from yeast and *orizanin* from rice polishings, both being identical in chemical, physical and biological properties. Kuhn and his colleagues have isolated from yeast a blue fluorescent substance which they named *thiochrome*. For standardisation, 10 mg. of a concentrate prepared from rice polishings have been designated as one International unit. One of the chief effects of partial deficiency of this vitamin is the production of intestinal stasis, resulting in the retention in the bowels of the putrid food residue and absorption of the products of putrefaction. Its absence in the food causes beri-beri in man and analogous disease in animals. This assertion has of late been challenged by Drummond and Woollard who hold that the symptoms of polyneuritis are really due not to the absence of vitamin B_1 but to partial starvation as a result of loss of appetite which is characteristic of the absence of this vitamin.

It is found to some extent in all natural food-stuffs, specially in the green and outer layers of cereals and legumes, in yeast and nuts. It is also present in tomatoes, oranges, green leaves, fish, meat, eggs and milk. It is absent in white bread but present in whole-meal bread. Marmite is a valuable source of vitamin B and is used in the treatment of pernicious anæmia. It is probable that the large proportion of chronic disorders of the alimentary tract are really due to the deficiency of this vitamin in the diet.

The antineuritic vitamin is slightly affected by high temperatures. It is however less stable than vitamin A, although it withstands boiling for a short time and is destroyed slowly in acid or neutral solution even when subjected to a high temperature. It is probable that it also contains a growth-promoting factor.

(*c*) *Antiscorbutic Vitamin, or Water-soluble C.*—This is necessary for the prevention of scurvy and is found in fresh vegetable and animal food. It has been isolated in a crystalline form which has been named *hexuronic* or *ascorbic acid*, originally found in the cortex of the suprarenal gland. Its richest sources are cabbages, turnips, lemons, oranges and tomatoes. Milk and meat possess a definite but low antiscorbutic value. The antiscorbutic vitamin differs from the antineuritic one in its distribution and properties, as well as in the nature of its influence on nutrition. This vitamin is less widespread and is more sensitive to heat and drying than the antineuritic one. Tinned foods which have been raised to a temperature of 120°C. lose their antiscorbutic properties. It has also been shown that although dried pulses contain no antiscorbutic principles while still dry, the antiscorbutic elements develop in 48 hours if they are moistened, kept warm and allowed to germinate. All dry foodstuffs are deficient in antiscorbutic vitamin. The tissues of fresh vegetables dried at a low temperature, or their expressed juices preserved in the cold rapidly lose their antiscorbutic property.

(*d*) *Antirachitic Vitamin, or Fat-soluble D.*—McCollum has pointed out that this vitamin, which was considered the same as the fat-soluble A factor, is a separate entity. It can be produced by the exposure of ergosterol to ultra-violet light and is now obtainable in pure form as white needle-like crystals, which has been named *calciferol*. Webster and Rosenheim have pointed out that *ergosterol*, a highly unsaturated sterol, is the direct precurser of vitamin D and that this substance is transformed into vitamin D, when the skin is exposed to direct sunlight. Moreover Steenbock and Drummond have shown that substances which were previously inert become activated and possess antirachitic virtue when exposed to ultra-violet rays. Vitamin D is more resistant to heat and oxidation than vitamin A.

Deficiency of this vitamin retards absorption of calcium from the intestine and thus causes rickets. In fact even when the calcium-

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phosphate ratio in the food is normal, deficiency of vitamin D results in imperfect formation of bone and teeth which are rectified by the supply of this vitamin.

Cod-liver and halibut-liver oils contain vitamin D in very large amounts. Butter fat has a much greater effect on xerophthalmia than cod-liver oil, whilst the antirachitic power of cod-liver oil is far superior to butter fat. The antirachitic property of cow's milk can be increased by exposing the cow to sunlight, but the growth promoting property remains the same.

(*c*) *Anti-sterility Vitamin, or Vitamin E.*—Evans has shown that there is a third fat-soluble factor necessary for reproduction. Absence of this vitamin in the food causes death of the products of conception These observations were made on female rats and recently it has been reported that administration of wheat-germ oil to women with history of sterility or repeated abortion caused them to conceive and give birth to normal living children.* It is present in most animal tissues but not to a high degree and is not present in cod-liver oil. Milk fat contains very little of this vitamin. It is found in abundance in the embryos of seeds and green vegetables, chiefly lettuce, alfalfa, peas, oats, corns and wheat-germ oil.

(*f*) *Pellagra Preventive Vitamin, Vitamin* B_2 *or G.*—This is vitamin *p-p* of Goldberger. Animals deprived of this vitamin show retardation of growth and a group of symptoms resembling pellagra. Although it is generally admitted that pellagra in man is due to faulty diet, there are strong indications that several factors may jointly operate to produce the condition, and one of these is vitamin B_2 or G. In fact Aykroid has pointed out that although rice, millet and maize are deficient in vitamin B_2, human pellagra is associated with the consumption of maize only. It is believed that vitamin B_2 is related to the anti-anæmic factor contained in the liver.

Vitamin Preparations

Irradiated Ergosterol, Cod-liver Oil, Halibut-liver Oil, Yeast

LIQUOR ERGOSTEROLIS IRRADIATI

Solution of Irradiated Ergosterol

Syn.—Viosterol; Radiostol.

Source.—It is a solution in oil of an antirachitic principle, probably identical with the vitamin D contained in cod-liver oil. Contains 3000 units of antirachitic activity in 1 G. Prepared by submitting a solution of purified ergosterol in a suitable solvent to the action of ultra-violet radiation from a mercury vapour lamp, or from some other suitable source for a limited period of time, and dissolving the whole product in some vegetable oil (arachis oil).

The International Unit of vitamin D is the antirachitic activity of 0.001 grm. of standard solution prepared by the British Medical Research Council. 1 mgrm. of pure Calciferol has an antirachitic activity of 40,000 Units.

B.P. Dose.—*Prophylatic for an infant,* **1000 to 3000 Units (0.3 to 1 mil or 5 to 15 ms.) daily.** *Curative* **daily dose for an infant, 5000 to 10,000 Units (1.5 to 3 mils or 25 to 50 ms.).**

Pharmacology and Therapeutics

The utility of vitamin D has been fully discussed. Irradiated ergosterol is rich in vitamin D and possesses antirachitic property of great power. It helps absorption of calcium and therefore its use should be supplemented by

* British Medical Journal, April 18, 1936

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the use of that element. Apart from its use in rickets, it is of great value in helping development of bones and checking caries of tooth, both as a prophylactic and also as a curative agent, which Mellanby has shown to be due to deficiency of vitamin D.

In animals large doses cause deposits of calcium in the vessels, heart, stomach, colon, kidneys, and lungs, and help formation of calcium phosphate calculi. Toxic symptoms are nausea, vomiting, diarrhœa, loss of weight, malnutrition, fever and even nephritis. Spleen and the thymus are atrophied, the animal loses weight rapidly and finally dies.

OLEUM MORRHUAE

Cod-liver Oil

Syn.—Oleum Jecoris Aselli.

Syn. I.V.—*Macher tel*, Beng. *Machli ka tel*, Hind.

Source.—The oil extracted from the fresh liver of the cod, *Gadus morrhua*, and from which solid fat has been separated by filtration at about 0°C.

Characters.—Pale yellow, with a slight fishy but not rancid odour. Sp. gr. 0.922 to 0.929. *Solubility.*—Readily in ether and chloroform, and slightly in alcohol (90 p.c.).

Composition.—The chief constituents are *Vitamins A* and *D*, also (1) *Jecolein* and *therapin*, the glycerides of unsaturated acids. (2) *Palmitin* 4 p.c. (3) Free *fatty acids* (oleic, palmitic, stearic). (4) Traces of *cholesterol* and *bile acids*. (5) Trace of *iodine*, *bromine*, *sodium*, *calcium*, *potassium*, *iron*, *phosphorus* in organic combinations. (6) Several *alkaloids* such as morrhuine, aselline. (7) *Resinous matter*. (8) *Colouring matter*.

B.P. Dose.—30 to 120 ms. or 2 to 8 mils.

Official Preparation

1. **Extractum Malti cum Oleo Morrhuæ.**—Contains about 36 ms. of cod-liver oil in 240 ms. **B.P. Dose.—60 to 240 ms. or 4 to 16 mils.**

Non-official Preparations

1. **Emulsio Olei Morrhuæ, B.P.C.**—Cod liver oil 50; acacia powder 12½; tragacanth powder 0·6; elixir of saccharin 0·2; chloroform 0·2; water to 100. *Dose.*—2 to 8 drs. or 8 to 30 mils.

2. **Emulsio Olei Morrhuæ cum Hypophosph., B.P.C.**—Contains 50 p.c. cod-liver oil. Being free from sugar is suitable for diabetic patients. *Dose.*—2 to 8 drs. or 8 to 30 mils.

3. **Ostelin.**—A glycerin suspension of irradiated ergosterol; contains 5000 International units of vitamin D per mil in easily assimilable form. Powerful antirachitic; 4 drops equal to 1 dr. of cod-liver oil. Useful in all conditions where cod-liver oil is indicated. Miscible with water.

4. **Sodium Morrhuate.**—Sodium salts of the unsaturated fatty acids of cod-liver oil after extraction by ether. Used in *tuberculosis* and *leprosy*. *Dose.*—½ to 5 c.c. of a 5 p.c. solution subcutaneously, 2 to 3 times a week until febrile reaction occurs.

Pharmacology

Externally.—Cod-liver oil is a bland unirritating oil freely absorbed through the skin.

Internally. **Gastro-intestinal tract.**—On account of its fishy, unpleasant smell, many patients cannot retain it, and

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with some it causes indigestion. In large doses, it may cause diarrhœa, the oil being expelled in the stools. Cod-liver oil is more rapidly absorbed than other oils, fats, butter, *ghee*, etc. It is also better digested, because the free acids it contains facilitate its emulsification and saponification by its admixture with the alkaline secretions of the pancreas, the intestinal glands and bile. Along with the cod-liver oil, other oils and nitrogenous elements of the food are helped in their digestion, and are also better absorbed by the lacteals. But the value of cod-liver oil depends upon the fact that the liver decomposes fats and yields to the blood "unsaturated" fatty acids which are capable of exerting chemical action more markedly. An increase in the amount of these acids tends to disintegrate the tubercle bacillus.

Tissues and metabolism.—Cod-liver oil is not only quickly absorbed and readily assimilated, but enters into permanent combination with the body cells yielding energy to them. It is therefore a **food**; a tablespoonful yielding about 130 calories. Iodine, bromine, phosphorus, etc., perform their share when administration is continued for a long period. But the specific action of cod-liver oil depends upon the unsaturated fatty acids which serve the immediate needs in the production of energy; the saturated acids are stored in the nature of a reserve. It also oxidises readily in the tissues, checks the wastage of other nitrogenous elements and promotes healthy cell formation and increases body weight. The value of cod-liver oil is really due to the presence of vitamins A and D which are essential for the nutrition and growth of young animals, and for correcting improper balance of calcium and phosphorus intake. Moreover the presence of unsaturated fatty acids and vitamin D helps absorption of calcium (*see* page 95). The true vitamin factor is contained in the 1 p.c. of the nonsaponifiable matter contained in the oil.

The superiority of cod-liver oil over other oils depends chiefly upon (1) rapid absorption, (2) quick assimilation, (3) ready oxidation, (4) higher nutritive value, (5) high vitamin content, and (6) its powerful effect on cell-growth and metabolism. Therefore many morbid conditions of the system due to faulty assimilation and defective oxidation are slowly removed by it.

Elimination.—It is mostly absorbed, a little is expelled in the fæces. Some of the acid ingredients escaping through the skin may produce a sort of acne.

Therapeutics

Externally.—If the oil is not retained, or creates indigestion or diarrhœa, inunction is a good method for introducing it into the system. Wasting diseases of children are

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specially benefited by this method, the only drawback being its objectionable odour.

Internally.—It is of signal service in all sorts of chronic wasting disease dependent on malnutrition and mal-assimilation, especially so in scrofulous disease in its various forms, and phthisis, caries of bones, chronic joint disease, *e.g.* rheumatic or scrofulous arthritis, long-continued suppuration, chronic bronchitis, general debility due to under-feeding, exhaustion, overwork, etc. Convalescence from acute illness, *e.g.* pneumonia, etc., are benefited under its course. As a nourisher and restorer of nerve-cells, it is of great value in old age, debility or exhaustion.

Being rich in vitamins A and D, it is pre-eminently suited for promoting growth and nutrition, and preventing rickets and defective calcification of teeth. As it contains iodine (0.0001 p.c.) its use has been suggested in the treatment of goitre, which is supposed to be due to deficiency of iodine in the food.

Sodium morrhuate is used as a **sclerosing agent** in the treatment of varicose veins, hydrocele and varicocele. For varicose veins ½ to 1 c.c. of a 5 p.c. solution is injected at each puncture, and a total of 5 c.c. is given spread over a fortnight. For hydrocele the sac is washed out with sterile water after the fluid has been aspirated, and 4 to 5 c.c. of a 5 p.c. solution is injected through the canula, the puncture closed with collodion and the scrotum massaged for a few minutes. A second tapping and injection is necessary, after which the scrotum becomes normal within three months.

Contra-indications.—Indigestion, nausea, vomiting, eructation, diarrhœa, gastric catarrh, high temperature, severe hæmoptysis, contra-indicate its use.

Mode of administration.—It should be commenced with small doses, say 1 dr. and gradually increased to 4 drs., and given after food twice or thrice daily. In the beginning, say for one week, it is a good plan to give only one dose a day preferably after dinner.

Brown oil is superior to pale oil because it contains more fatty acids but its disagreeable smell and taste are a drawback. Children generally can take it better, or soon get accustomed to its taste, but in the majority of cases a pleasant combination becomes necessary. Saponification should be avoided on account of the chemical changes that would occur with the fatty acids contained in the form of glycerides. In fact the great *point is to preserve these acids absolutely unchanged.* Hence, emulsification, as in Emulsio Olei Morrhuæ, B. P. C. is to be recommended. It can be extemporaneously emulsified by gum acacia or tragacanth, sweetened with glycerin and flavoured by lemon. It can also be given in flexible capsules, mixed with isinglass

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jelly, or still better with extract of malt. Some patients prefer to take it on milk, coffee, wine or orange juice. A pinch of salt placed on the tongue, a cut lemon sucked, a piece of fresh ginger well chewed, and some of the juice swallowed before and after the dose, effectively remove the nauseous taste in many instances. To help its emulsification as well as to stimulate the pancreatic secretion, purified ether (10 to 20 ms.) is sometimes combined with it.

Halibut-liver Oil.—The oil expressed from the liver of halibut (*Hippoglossus hippoglossus linnaeus*). Contains high concentrations of vitamins A and D. The vitamin A content as measured by the blue unit test is fifty times greater than cod-liver oil, while the vitamin D content is several times greater than that of cod-liver oil. Largely used in place of cod-liver oil and is free from any strong and unpleasant taste. *Two to three drops provide the vitamin equivalent of a teaspoanful of cod-liver oil.*

CEREVISIAE FERMENTUM

Yeast. (*Not official*)

Syn.—Faex Medicinalis. Beer Yeast. Saccharomyces Cerevisiæ.

Characters.—A viscid, frothy liquid, having a peculiar odour and bitter taste.

Composition.—Several enzymes: (1) *Zymase*, which decomposes monosaccharides into alcohol and CO_2; (2) *Invertase*, which inverts sugar; (3) *Maltase*, converts maltose into dextrose; and (4) *Endotryptase*, a proteolytic enzyme. Fats, *ergosterol*, various carbohydrates, and various proportions of proteins combined with nucleic acid forming nucleins and nucleo-proteins. (5) *Water-soluble vitamin B* complex.

Dose.—Of compressed yeast, 1/4 to 1/2 oz. or 8 to 16 grms.; of dried yeast, 1/2 to 1 dr. or 2 to 4 grms.

Non-official Preparation

1. **Nuclein.** *Syn.*—*Nucleol*—Obtained from yeast. A combination of nucleinic acid with albuminates and carbohydrates. *Dose.*—15 grs. several times daily. Recommended in *tubercle, cancer* and various *septicæmic conditions.* Its value is doubtful. **Tablets.**—1 gr.

Pharmacology and Therapeutics

Yeast soap or yeast combined with ichthyol and salicylic acid is useful in acne and dermatitis.

The action of yeast is that of nuclein and it is both a **leucocyte-stimulant** and **bactericide.** It is credited with some power to neutralise toxins present in the blood. Both brewer's and compressed yeast are gastro-intestinal antiseptics, increase intestinal peristalsis, clear the tongue and aid in combating streptococcic and staphylococcic infections. In addition to *nuclein*, yeast contains many *enzymes*, and it gives rise to many other products, partly as a result of fermentation and partly by its action upon the metabolism of liver cells, and is supposed to diminish sugar in diabetes. It has been recommended in the treatment of furunculosis (both by mouth and locally), gastro-enteritis, and constipation. Being rich in *antineuritic vitamin* it is used in **beri-beri.** Yeast may be used either with meals or on an empty stomach, suspended in water or orange juice. The yeast cake may be used in solution in water; the dose being half to one-third of a cake. It may also be administered either in the crude form as obtained from the brewers, or as **Marmite.** Because of the presence of ergosterol, yeast when irradiated with ultra-violet light, acquires anti-rachitic properties owing to the conversion of ergosterol into

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witamin D. Recently the use of marmite has been extolled in the treatment of **macrocytic anæmia**, specially the anæmia of pregnancy. Since dried yeast, or watery extract of yeast, is therapeutically inactive as a source of extrinsic factor, but autolysed yeast products are active, it has been suggested that the anti-anæmic factor is manufactured during the process of autolysis which is possibly a protein breakdown product of the nature of a polypeptide.

SUCROSUM

Sucrose

Syn.—Saccharum Purificatum ; Refined Sugar ; Cane Sugar.
Syn. I. V.—*Misri*, *Chini*, Beng.
Source.—Obtained from the juice of the *sugar-cane*, or of the *sugar-beet*.
Characters.—Colourless crystals or crystalline masses, or a white powder ; no odour ; taste, sweet. Readily *soluble* in water forming a clear, colourless and odourless syrup.
Enters into.—The preparation of all syrups.

Action and Uses

Sugar is a **food**, and tends to produce fat and to maintain body-heat and is used in wasting diseases. It is a demulcent and preservative, and may be given in irritant poisoning, but it is mostly used as a basis of various refrigerant beverages and sherbets. In the form of syrup it is added to various pharmaceutical preparations to cover the disagreeable taste of drugs.

Part of it is decomposed in the gut with the formation of acid and gas. It delays digestion and favours development of hyperacidity. Sugar is a valuable **diuretic** and removes œdema. In the blood it produces a transitory hyperæmia by osmosis, and like salts and urea hinders absorption of water from the tubules.

LACTOSUM

Lactose. $C_{12}H_{22}O_{11},H_2O$

Syn.—Saccharum Lactis ; Milk Sugar.
Source.—Obtained from the whey of milk.
Characters.—A white, crystalline powder. Odourless ; taste, faintly sweet. *Solubility.*—1 in 7 of cold, more in hot water.

Non-official and Allied Preparations

1. **Human Milk, Artificial.**—New milk 30, cream 1¾, milk sugar 1½, water 18.

2. **Koumiss, Artificial.**—True koumiss as prepared by the Tartars is a fermented mare's milk. Artificial koumiss may be brewed at home from cow's milk by the following process. Dissolve grape sugar ½ oz. in water 4 ozs. and yeast 20 grs. in cow's milk 4 ozs. Pour them into a quart bottle, and fill up with milk. Cork and wire it well, and leave it in a cool place with occasional shaking.

Koumiss is an easily assimilable nutritious food and remedy, valuable in the *wasting disease of the lungs*, in which case it can be taken *ad libitum*. It is borne by stomachs which refuse cod-liver oil. It is also very useful in *dyspepsia*, *infantile diarrhœa* and *kidney disease*.

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3. **Kephir.**—Is a fermented milk like koumiss, the ferment being a Caucasian mushroom. It can also be made at home by kephir-ferment, adding a fungus which contains yeast and *Bacillus acidi lactici*.

4. **Somatose.**—Desiccated albumoses. Prepared either from milk or meat. Greatly assists *lactation* and when combined with iron as in **Ferro-Somatose**, is useful in *chlorosis* and *anæmia*.

5. **Dried Milk.**—As a food for infants dried milk has almost entirely superseded "humanised milk." It is the residue left after the natural moisture in milk has been evaporated. When required for use boiled water is added to it.

Pharmacology and Therapeutics of Lactose

Internally.—Lactose is a valuable nutrient, and being less sweet than cane sugar is largely used. It greatly increases the flow of urine and is therefore given in cardiac and renal dropsies. It is largely used in humanising cow's milk for infants and because it does not ferment in the stomach it is the best sweetening agent in infantile dyspepsia and irritable conditions of the stomach. It is considered to be a physiological accelerator of labour pains and for this purpose doses of 5½ to 7 drs. may be given dissolved in half a pint of milk. Sterile milk is used in foreign protein therapy intramuscularly (*see* Protein Therapy).

On account of its hardness lactose is used to facilitate the minute subdivision of other drugs, or to dilute potent substances and bring them up to a uniform standard.

DEXTROSUM

Dextrose. $C_6H_{12}O_6$

Syn.—Grape Sugar.

Source.—May be prepared from starch by hydrolysis. In white, crystalline or granular powder; odourless; taste, sweet. *Soluble* in less than 1 part of water, in 50 parts of cold alcohol (90 p.c.), in 5 parts of boiling alcohol (90 p.c.).

GLUCOSUM LIQUIDUM

Liquid Glucose

Syn.—Corn Syrup.

Source.—Obtained by the hydrolysis of starch, and consists of a mixture of dextrose, maltose, dextrin and water.

Characters.—A colourless, or almost colourless, viscous syrup; odourless; taste, sweet. Freely mixes with water forming a clear solution; *partly soluble* in alcohol (90 p.c.).

Official Preparation

1. **Syrupus Glucosi Liquidi.** *Syn.—Syrup of Glucose.*—33·3 p.c.

Pharmacology and Therapeutics

Dextrose is rapidly absorbed when administered by the mouth. Given by the rectum or subcutaneously it does not raise the sugar in the blood so easily. Thus Hopkins found that while dextrose given *per os* produced hyperglycæmia

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in half an hour, it took four and a half hours when given subcutaneously in 5 dr. doses. A definite rise of blood-sugar occurs when given as rectal injection with saline. It undergoes oxidation in the body rapidly, but this depends upon the availability of insulin, and in the absence or deficiency of insulin it cannot be utilised.

Given by the mouth it is of great value in nervousness and subnormal health in infancy supposed to be due to shortage of sugar, in asthmatic attacks of children, and malnutrition. By sparing the protein from destruction and assisting the metabolism of fats, dextrose counteracts acidosis or prevents its onset and is used as a preliminary to volatile anæsthesia to replenish the carbohydrate reserve and to avoid acidosis and delayed chloroform poisoning. It is given intravenously to combat severe toxæmias, as for instance in pernicious vomiting of pregnancy, uræmia, eclampsia, etc. A 5 p.c. solution is approximately isotonic and may be used intravenously to increase the volume of blood in the treatment of **shock** following operations, **collapse of cholera,** and as a **circulatory stimulant** in acute infectious fevers. It is more valuable than the ordinary injection of normal saline solution, and may with advantage be combined with strophanthin in circulatory failure. Tubes containing glucose solutions for intravenous use are available in the following strengths, *viz.*, 12½ p.c., 25 p.c., and 50 p.c., containing 10 to 200 c.c. each.

By raising the glycogen content it protects the liver from damage in poisoning by cinchophen, chloroform, arsphenamine, phosphorus and heavy metals.

Glucose is a valuable article of diet in **enteric fever.** It is easily absorbed from the rectum better than any other food, and is therefore largely used in the treatment of **gastric ulcer,** the patients being given 3 to 4 pints daily of saline sugar solutions thus giving the ulcers every chance of healing. It is also a valuable means of preventing hypoglycæmia which may follow an overdose of insulin in the treatment of diabetes, when it is combined with bicarbonate of soda. Similarly when given with insulin it is valuable in ketosis or coma of diabetes. Intravenous injection of hypertonic glucose (25 p.c. is strongly hypertonic) causes a temporary reduction in the fluid pressure in the tissues by the withdrawal of water and is used in arterial hypertension, and to **reduce intracranial pressure** in meningitis, fracture of the skull, etc. The solution should be freshly prepared and kept slightly above the body temperature and the injection made very slowly. Recently Shirley Smith recommended its use orally with injections of insulin in the treatment of cardiac affections and angina.

5 to 10 c.c. of a mixture containing equal parts of dextrose 50 p.c. and sodium chloride solution 30 p.c. used at

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one injection is by some considered as the best treatment for varicose veins. The solution should be left in contact with the endothelium for at least 5 minutes with a vein occluder, and subsequently strapped with a gauge pad to compress the vein.

LAEVULOSUM

Lævulose

Syn.—Fructose.

Source.—Prepared from invert sugar, or from honey. Contains lævulose together with small quantities of dextrose and water.

Characters.—A white or cream coloured, hygroscopic, crystalline powder. Odourless; taste, sweet. Freely *soluble* in water.

Action and Uses

Lævulose is more sweet than cane sugar and is more easily assimilated. Like other lævorotatory carbohydrates it is utilised by diabetics and has therefore been used without increasing the excretion of sugar. It is largely used in wasting diseases, specially tuberculosis and scrofula, when as much as several ounces are taken daily.

In normal healthy persons all ordinary sugars, glucose, etc., when administered raise the concentration of the blood-sugar, but not lævulose, if the liver is healthy. If therefore there is a definite lesion in the liver, lævulose acts like ordinary sugar, *i.e.*, there is a marked increase of blood-sugar. It is therefore used for testing liver function. After a fast of 12 hours a dose of 50 grms. is administered dissolved in 4 to 5 oz. of water, and the blood-sugar is estimated every half hour for two hours. A rise of 0.03 p.c. above the fasting level indicates hepatic disorder.

GELATINUM

Gelatin

Source.—The air-dried product of the action of boiling water on such animal tissues as skin, tendons, ligaments, and bones.

Characters.—In translucent, almost colourless, sheets or shreds. A solution in 50 parts of hot water solidifies to a jelly on cooling. Insoluble in alcohol (90 p.c.) and in ether. Tannin precipitates it.

Official Preparation

1. **Gelatinum Zinci.** *Syn.—Unna's Paste.*—Zinc Oxide 15 p.c., Gelatin 15 p.c.

Uses

Gelatin is used as a basis for several pharmaceutical preparations such as suppositories, pessaries, bougies, discs, gelatin capsules, and as a coating for pills. It is largely employed in dietary for making jellies, etc.

It is a powerful protein sparer; being able to save from destruction half its weight of protein, or twice as much as is spared by an equal quantity of carbohydrate. One gramme

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yields about 4.5 calories. It appears that its value as a protein sparer has been exaggerated. As it does not contain cystin and tryptophan it cannot supply the whole protein need of the body. But when given with other foods, specially with milk it forms a valuable food.

Gelatin is used internally chiefly for its hæmostatic effect. Injection into the gluteal region of sterilised solution of gelatin in physiological salt solution (1 to 2 p.c.) promotes the formation of clot and has been advocated for the treatment of aneurism and internal hæmorrhages to increase the coagulability of blood. Tubes of sterile concentrated saline gelatin solution are prepared for the purpose. Particular care should be taken to see that the solution is absolutely sterile, as several cases of tetanus are on record, specially because some specimens of gelatin contain tetanus spores. The treatment however is unreliable and sometimes dangerous. For its colloidal value it is often used with saline infusions in the treatment of collapse and shock; but as has been pointed out elsewhere (*see* page 83) it may cause dangerous symptoms of anaphylactoid reaction producing respiratory distress and cardiac dilatation.

Medicinally it acts as a hæmostatic, due to an admixture of lime, 0.6 p.c. in solution. A 5 p.c. to 10 p.c. solution may be locally used in wounds, epistaxis, etc.

LECITHIN

(Not official)

Syn.—Ovo-Lecithin.

Source.—It is a normal constituent of brain substance and is obtained from yolk of egg. In yellowish wax-like substance, insoluble in water.

Dose.—By mouth, 3 to 8 grs. or 0·2 to 0.5 grm.; hypodermically, ¾ to 2 grs. in sterile olive oil.

Non-official Preparations

1. **Elixir Ovolecithini, B.P.C.**—Contains 1 gr. of ovolecithin in 1 dr. *Dose.*—1 to 4 drs. or 4 to 16 mils.

2. **Pilulæ Ovolecithini, B.P.C.**—Each pill contains 1½ grs. lecithin and ¹/₆₀ gr. strychnine hydrochlor. with althæ, liquorice root, gum acacia, alcohol and glycerin. *Dose.*—1 to 4 pills.

Pharmacology and Therapeutics

Lecithin is broken up by the pancreatic juice into glycerophosphoric acid, fatty acids, and choline. It is used chiefly for its supposed action in improving the nutrition of the nervous system. It is also stated to increase the number of red blood-corpuscles and to raise their hæmoglobin content. It increases body-weight and improves general nutrition.

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GROUP XXI

ALTERATIVES IN GOUT

Guaiacum, Colchicum, Cinchophen

GUAIACI RESINA

Guaiacum Resin. *(Not official)*

Characters.—In large masses or sometimes in rounded tears, yellowish-green to reddish-brown; brittle; fracture, vitreous. Thin splinters, transparent. Powder, greyish but becomes green by exposure to light and air. Odour, on warming somewhat aromatic; taste, slightly acrid. *Solubility.*—About 90 p.c. in alcohol (90 p.c.).

Composition.—Contains several resin acids, (1) *α* and *β-Guaiaconic acids* (70 p.c.), *Guaiacic* and *Guaiaretic acids*, and (2) *Guaiac β-resin*.

Dose.—5 to 15 grs. or 0.3 to 1 grm.

Non-official Preparations

1. **Mistura Guaiaci.**—Guaiacum resin 25 gm., sugar 25 gms., powdered tragacanth 5 gm., cinnamon water *q.s.* to 1000 mils. *Dose.*—½ to 1 oz. or 15 to 30 mils.

2. **Tinctura Guaiaci Ammoniata.**—Guaiacum resin 200 gms., oil of nutmeg 3 mils., oil of lemon 2 mils., strong solution of ammonia 75 mils., alcohol (90 p c.) to 1000 mils. *Dose.*—30 to 60 ms. or 2 to 4 mils.

3. **Confectio Guaiaci Co., B.P.C.** *Syn.—Chelsea Pensioner.*—Guaiacum resin 1, rhubarb 2, acid potassium tartrate 7.50, nutmeg 1, all in powder, sublimed sulphur 14.50. Mix together and add gradually purified honey 74. *Dose.*—60 to 120 grs. or 4 to 8 grms.

Action and Uses

Guaiacum is rarely used now, although in the form of Chelsea Pensioner it is still popular in the treatment of chronic rheumatism and gout. It is supposed to be a specific in gout, but is more useful as a prophylactic in the intervals of gouty attacks. The mixture is more popular than the tincture.

COLCHICI CORMUS

Colchicum Corm

Source.—The fresh corm of *Colchicum autumnale*, collected in early summer; or the same stripped of its coats, sliced transversely and dried at a temperature not exceeding 65° C.

Characters.—*Fresh corm.*—35 mm. long, 25 mm. broad, conical, hollowed on one side where it has a new corm in process of development, rounded on the other; outer coat, thin, brown, membranous; inner coat, reddish-yellow. Internally white, solid, yielding bitter disagreeable whitish turbid juice. *Dried slices*—2 to 3 mm. thick, yellowish at circumference, reniform, firm, whitish, amylaceous. Taste, bitter. No odour.

Composition.—(1) *Colchicine,* 0.4 p.c. an active alkaloid. (2) *Starch*, gum, sugar, tannin, etc.

Incompatibles.—Astringents, tincture of iodine, and guaiacum.

B.P. Dose.—2 to 5 grs. or 0·12 to 0·3 grm.

Official Preparation

1. **Extractum Colchici Siccum.**—Contains 1 p.c. colchicine, or $\frac{1}{100}$ gr. in 1 gr. **B. P. Dose.—¼ to 1 gr. or 0.015 to 0.06 grm.**

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COLCHICI SEMEN

Colchicum Seed

Source.—The dried ripe seeds of *Colchicum autumnale.*

Characters.—2 to 3 mm. in diameter, subglobular, slightly pointed, rough, reddish-brown, hard, tough, minutely pitted. Endosperm oily. Taste, acrid, bitter. No odour.

Composition.—(1) *Colchicine* 0.3 to 0.6 p.c. (2) A fixed oil.

B. P. Dose.—2 to 5 grs. or 0·12 to 0·3 grm.

Official Preparations

1. **Extractum Colchici Liquidum.** *Syn.—Fluid Extract of Colchicum.*—Contains 0.3 p.c. w/v of colchicine, or $\frac{1}{10}$ gr. in 5 ms. **B.P. Dose.—2 to 5 ms. or 0.12 to 0.3 mil.**

2. **Tinctura Colchici.**—0.03 p.c. w/v of colchicine, or $\frac{1}{250}$ gr. in 15 ms. **B. P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**

Non-official Preparations

1. **Colchicina, U.S.P.**—Pale yellow, amorphous scales, or powder. *Dose, U.S.P.*—0.0005 grm. or $\frac{1}{120}$ gr.

2. **Colchicine Salicylate.** *Syn.—Colchi-sal.*—A yellow powder, soluble in water. *Dose.*—$\frac{1}{120}$ to $\frac{1}{30}$ gr. or 0·0005 to 0·002 grm.

Pharmacology

Externally.—Locally applied to the skin and mucous membrane colchicum acts as an irritant, producing redness and smarting. Inhaled, its powder causes sneezing and watering of the eyes.

Internally. **Gastro-intestinal tract.**—Given by the mouth or injected hypodermically colchicine increases the gastric and the intestinal secretion, but this effect is not observed in every case. In moderate doses it causes purging, vomiting and abdominal pain. In large doses it is a powerful gastro-intestinal irritant. These symptoms appear several hours after administration even if the dose is large. This is probably due to the conversion into oxydicolchicine. According to Dixon colchicine acts on the intestine in the same way as pilocarpine and is antagonised by atropine. This however does not explain the whole action, *e. g.*, acute inflammatory reactions, which are really due to the irritant action of the drug on the mucous membrane, or as Fuehner and Rehbein have pointed out being due to capillary vasodilatation produced by the drug either directly or through excretion.

Nervous system.—Its action here resembles those of heavy metals or some bacterial poison, some however attribute them to collapse resulting from severe irritant action on the alimentary tract. Later there is both motor and sensory paralysis, and death takes place from respiratory and vaso-motor paralysis.

Circulation and respiration.—It depresses the circulation, lowers the blood-pressure and slows the respiration.

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The pulse becomes feeble, soft and rapid. These effects are probably due not so much to the colchicine acting on the cardiac and respiratory organs, as to the consequences of severe gastro-enteritis.

Kidneys.—Its action on the kidneys is uncertain. In some there is anuria, in others there is an increase of urine. The urinary constituents are not affected.

Acute toxic action.—The chief symptoms are those of gastro-intestinal irritation in a grave form. Violent burning in the throat, œsophagus and stomach; intense thirst; severe colic with vomiting and purging; the stools being first serous, then slimy and finally bloody; great prostration, rapid, feeble and thready pulse; cold skin bedewed with sweat; slow and laboured respiration and lastly death during collapse from respiratory paralysis; consciousness not being lost.

Antidotes.—Emetics, followed by demulcent drinks, as white of egg freely diluted with water. Tannic acid is a chemical antidote. Stimulants, tea, and coffee; morphine hypodermically.

Chronic toxic action.—Small medicinal doses long continued, bring about furred tongue, disagreeable taste, loss of appetite, thirst, epigastric pain, flatulence, and diarrhœa.

THERAPEUTICS

Internally.—Striking results follow administration of colchicum in acute gout. The severest pain and inflammation are removed in a few hours after 15 to 30 ms. of the tincture of colchicum. It succeeds well in first attacks on robust patients, but cannot prevent a relapse even if it is continued during the interval between the attacks. How it acts in this disease is not known. Garrod has experimentally shown that colchicum can in no way influence the elimination of uric acid in gouty people. Besides its specific property in gout, colchicum is useful in many other complaints of gouty people, such as dyspepsia, headache, hepatic congestion, neuralgia, etc. It affords no relief in the chronic gout of old debilitated persons. Rheumatism is never benefited.

Caution.—It should be avoided or given with great caution to the weak, the infirm, and those who suffer from cardiac weakness, chronic diarrhœa, chronic dysentery or colic.

Prescribing hints.—Colchicum may be administered in *acute gout* in two ways—either in full doses, say 20 to 30 ms. of the tincture, repeated every 2, 3 or 4 hours, or in repeated small doses, say 10 ms. of the tincture, every 3, 4 or 6 hours while the pain lasts. It should never be combined with acids as they *intensify* its irritating property, while alkalies given with it mitigate the same. Ordinarily the tincture is used, but it should be noted that the tincture of the seeds is stronger than that of the corm. As it is a cardiac depressant, the bowels must always be kept open during a course of colchicum to prevent accumulation of the drug in the system.

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CINCHOPHENUM

Cinchophen

Syn.—Quinophan; Atophan; Agotan.

Source.—It is 2 phenylquinoline-4-carboxylic acid. Prepared by the interaction of pyruvic acid and benzylideneaniline. Contains not less than 90 p.c. $C_{16}H_{11}O_2N$.

Characters.—White, or yellowish, powder or crystals; almost odourless; taste, slightly bitter. *Insoluble* in water, soluble in about 120 parts of alcohol (95 p.c.), in 100 parts of ether, and in solutions of alkali hydroxides, carbonates and bicarbonates.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Pharmacology and Therapeutics

Its action resembles the salicylates, and it is a valuable *antipyretic, analgesic and antirheumatic.*

In therapeutic doses, even on a purin free diet, it increases the **elimination of urates and uric acid** and causes a fall in the uric acid content of the blood. It does not interfere with the uric acid formation excepting eliminating it in increasing amount. This effect continues as long as the drug is used. To prevent precipitation of urates, the urine should be kept alkaline by the administration of bicarbonate, acetate or citrate of potassium and sodium.

It is eliminated within 3 to 6 hours after ingestion.

Cinchophen is largely used in rheumatism and gout. In acute rheumatic fever it is given in 15 gr. doses 3 or 4 times a day. Such large doses do not cause nausea or irritation of the kidneys and are better tolerated when given with alkalies. In gout its effects are more marked in acute attacks, relieving both pain and swelling rapidly.

For its analgesic effect it is used in sciatica, headaches and neuralgias.

As a rule no untoward effects are noticed even when used in large doses. Occasionally *vertigo, jaundice, digestive trouble, anorexia, fever* and *urticarial eruptions* may appear. Cases of acute yellow atrophy of the liver have been recorded due either to individual susceptibility or uninterrupted use for prolonged periods. Albuminuria or any kind of nephritis should be regarded as contra-indication. If there is nausea or impairment of appetite its use should be withheld.

It should be taken *after meals* followed by a draught of water. Because of the danger of accumulation, the treatment should not be continuous, but should have periods of rest.

Toxic symptoms.—Severe jaundice with tender enlarged liver, definite hæmorrhagic rash, bilirubin and albumin in the urine, with pale stool without any bile were observed in a man who had 118 grammes in 41 days for chronic rheumatism. Coagulation time of the blood was increased (7 minutes), bleeding time was normal. During the illness nitrogen excretion was high (15 to 18 grammes daily)

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showing breakdown of tissue protein. Death from subacute yellow atrophy of the liver after 37½ grs. in five days have been reported by Fraser (*British Medical Journal*, 29th December, 1934). Toxic symptoms have been observed after doses ranging from 54 grs. in five weeks to 72,00 grs. in four months.

Treatment.—Stoppage of the drug and administration of dextrose 60 G. with 20 units of insulin twice a day followed by duodenal lavage and administration of magnesium sulphate. (*British Medical Journal*, Nov. 14, 1931. *Epitome*).

GROUP XXII

DRUGS ACTING ON METABOLISM

Metabolism is the sum total of the chemical exchanges taking place in the tissues through the medium of the blood. These exchanges represent two phases, *viz. anabolic* and *katabolic*. The changes by which the different food materials are utilised in the building of the body represent the anabolic or constructive phase; whereas the breaking down process by which the waste products are produced with liberation of heat and energy represent the katabolic phase. The products of oxidation are CO_2, urea, water, sulphate, etc., and these are excreted by the lungs, with urine, fæces and sweat. The oxygen taken up by the lungs plays a most important part and the physiological oxidation of the body cannot be separated from the general metabolic phenomena.

Metabolism therefore embraces all changes taking place in the body, and the most important factors concerned in the regulation of metabolism are food, exercise, light and air. Normally the anabolic and katabolic processes are more or less balanced; the income in food being balanced by the expenditure of carbon, nitrogen and water in the urine, stool, sweat and respiration.

The term *basal metabolism* is used to denote the amount of potential energy or heat required to maintain the heat of the body, activity of the heart, respiratory movements, etc., when in complete rest. It is the smallest energy output compatible with health. Basal metabolism is in proportion to the surface of the skin, and since a tall person has a larger skin area, he requires more heat and therefore more food to keep the temperature normal.

Since the body is undergoing constant changes, the elements which go to build and maintain the body must perforce be subject to similar changes. Food is therefore necessary for growth and to replace the wear and tear of the body. The proteins contribute to the formation and repair of tissues, regulate the absorption and utilisation of oxygen, and play an important part in the chemistry of nutrition. They are characterised by the presence of nitrogen. If the income of nitrogen received from the protein food is equal to the amount of nitrogen eliminated with the

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different excreta, the body is then said to be in nitrogen equilibrium. If less is eliminated, it implies that the body is storing protein, whereas if more is excreted then the body is losing protein. During the growing period and convalescence, less nitrogen is eliminated to enable the body to build up tissue. Under normal conditions our diet is so regulated that the nitrogen equilibrium is maintained at a constant level. Proteins stimulate metabolism and the specific dynamic action is the result of deamination of the amino-acid, glycin, etc.

Carbohydrates and fats play the same role in the body, being sources of heat and energy. Fat however may be stored up in the tissue as part of body fat, or may be synthetised with other substances to form more complex constituents of the body, *viz.* lipoids. Carbohydrate is oxidised in the body to supply the necessary heat and is stored up as glycogen in the liver and muscles to be doled out as sugar according to the requirements of the body for use in tissue metabolism. This important function may be disorganised through various causes, *viz.* injury to the central nervous system, and over secretion of the adrenals or hypophysis, and is regulated by the internal secretion of the pancreas.

The role of vitamins in the general metabolism is now widely recognised and diseases like rickets, beri-beri, scurvy and pellagra are regarded as the result of metabolic disturbances caused by deficiency of certain vitamins in the food. This has already been discussed (*see* page 557).

Inorganic metabolism.—Since most of the therapeutic measures depend for their action on the alteration they produce in the inorganic constituents of the body, a knowledge of the metabolism of the inorganic salts is a great help to the pharmacologist. Mineral salts form about one-twentyfifth part of the whole body. The chief mineral elements are calcium, sodium, potassium, magnesium, iron, manganese, zinc, copper, lithium and barium; phosphorus, sulphur, chlorine, silicon, fluorine, etc. Of these calcium, sodium, potassium, manganese, iron and copper are the most important and are the alkali forming elements; while phosphorus, sulphur and chlorine are the acid forming ones. These salts form an essential part in the composition of living matter and maintain a normal composition and osmotic pressure in fluids and tissues of the body and play an important part in the regulation of the acid-alkali balance (*see* p. 592). Sodium chloride occurs in all the tissues and fluids of the body. Since every cell contains phosphorus, it is essential for the multiplication of cells and growth of the body. The phosphates of sodium and potassium regulate the reaction of body fluids and tissues, control the osmotic pressure and inter-change of fluids. Calcium phosphate is

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essential for the development of bones, and calcium itself performs many important functions already discussed (*see* p. 97). Calcium metabolism is intimately related to vitamin D, parathyroid and thyroid, also on the reaction of the blood; acidosis helps retention of ionised calcium, while alkalosis produces tetany. Iron is an important element of hæmoglobin. It is also present in minute quantities in the muscles and other tissues where it helps the oxidation and catalysis of enzymes. Iodine is stored up as thyroxine in the thyroid gland and deficiency of iodine results in goitre.

Within recent years the effects of light and air on metabolism have received much attention owing to the admirable work of Sir Leonard Hill. He has shown that under cool open air condition the tone of the body is much increased, and the growth of infants becomes more rapid in the cool months. Exposure of the body to the cool atmosphere has a stimulating effect on the general metabolism, whereas heat has a depressing effect with a lower basal metabolism. A sufficiency of sunlight with cool, dry and moving air is conducive to health and gives a feeling of well-being. Light and air exert a much more important effect on the body metabolism. The ultra-violet rays of the sunlight are absorbed by the skin and forms vitamin D so important for the formation of bony skeleton and prevention of rickets. Similarly exercise by throwing more work on the muscle increases protoplasmic activity which implies supply of more nutrient material and oxygen.

THYROIDEUM

Thyroid

Syn.—Thyroideum Siccum; Thyroid Extract; Desiccated Thyroid Gland.

Source.—Prepared from the thyroid gland of oxen, sheep, or pigs. Remove the connective tissue and external fat from the glands; dry at temperature not exceeding 60°; powder; remove all fat by extraction with light petroleum, dry. Contains 0.1 p.c. of iodine in combination as thyroxine.

Characters.—A cream-coloured amorphous powder. Odour and taste, faint and meat-like.

B.P. Dose.—$\frac{1}{2}$ to 5 grs. or 0.03 to 0.3 grm.

THYROXINSODIUM

Thyroxine-sodium. $C_{15}H_{10}O_4NI_4N_a$

Source.—Prepared by the action of the limited amount of sodium carbonate upon thyroxine, obtained by the controlled hydrolysis of thyroid gland with barium hydroxide and subsequent purification, or by synthesis. Contains not less than 61 p.c. and not more than 65 p.c. of iodine.

Characters.—A white, crystalline powder. Sparingly *soluble* in cold water, freely in solution of sodium carbonate or hydroxide. Unstable in alkaline solution.

N.B. It should be dispensed when thyroxine is ordered

B.P. Dose.—$\frac{1}{610}$ to $\frac{1}{64}$ gr. or 0.0001 to 0.001 grm.

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Pharmacology

Thyroxine is a powerful poison. When thyroxine or thyroid extract is administered to normal persons no obvious effects are observed unless it is pushed to elicit toxic symptoms. The effects observed are quickening of the pulse, vomiting and diarrhœa, increased metabolism, particularly an increase of nitrogenous metabolism, loss of weight and emaciation. A single dose has very little effect, but small repeated doses produce toxic symptoms. In fact a single large dose even when administered intravenously does not produce any effect for 24 to 36 hours. Continued use tends to produce cumulative effects.

Internally. **Circulation.**—Given by the mouth for a prolonged period, thyroid causes increase in the pulse-rate, palpitation and weakness of the heart-beat. Sometimes no acceleration is observed even after its use for a long time. This is possibly due either to deterioration or to absence of thyroxine from the dried gland. The cause of acceleration is not clearly understood, and may be due to stimulation of the centre or to increased metabolism. Thyroid extract injected into the body causes a fall of blood-pressure, due, according to Dixon, to the presence of organic extractives. Given by the mouth it has no effect in reducing the blood-pressure. It increases the number of lymphocytes in the blood.

Metabolism.—Thyroid increases metabolism of the proteins, fats and carbohydrates even in normal animals, although it is more marked when it is low as in thyroid deficiency. The excretion of nitrogen and carbonic acid, and the consumption of oxygen, are increased, so that an excess of urea, uric acid and xanthin bases is eliminated through the kidneys and more carbonic acid by the lungs. In fact more nitrogen is excreted than is taken by the food, which implies that the excess is due to destruction of tissue protein, and since the glycogenic function of the liver is disorganised, the use of carbohydrate or fat does not check the protein destruction. As a result of all these effects the body temperature rises, and although the appetite improves the weight falls which is greater than can be accounted for by the loss of tissue protein. Cushny suggests that the most important factor in the reduction of weight is diuresis, which helps to eliminate a large amount of fluid not only in subjects of myxœdema but also in persons suffering from obesity.

The basal metabolism is increased about 2 p.c. by 1 mg. of thyroxine in adults weighing 150 pounds. In myxœdemic patients 10 mg. may produce an increase of 30 p.c. The results are the same whether thyroxine is given by the mouth or intravenously. If it is continued in large doses, symptoms of hyperthyroidism become marked by the 5th or 6th day.

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The normal human thyroid contains about 10 mg. of iodine, but this depends upon the quantity of iodine taken with food. When iodides are given this iodine is doubled. The gland is concerned in the development and maintenance of the normal functions of the body, and this it does by virtue of its internal secretion, which can only be formed when there is a certain amount of iodine in the food. It is possible that part of its activity is dependent upon the supply of adrenaline, and through its effect on the autonomic nervous system it increases the tone of the uterus and intestine (Bastedo). According to Bircher thyroid promotes the growth of bone in normal animals and for this reason has been used to promote union of bones in delayed healing of fractures.

Kidneys.—Thyroid is a powerful **diuretic**, but the exact manner of its action is not clear. The increased excretion of urea is partly responsible for the effect, although some attribute a specific action on the kidney. It is possible that the passage of a large amount of water and sodium chloride to the circulation produces hydræmia of the blood with consequent diuresis.

Nervous system.—Large doses sometimes cause tremors, restlessness and insomnia; and mania has been known to follow its use for the cure of obesity.

Excretion.—It is chiefly excreted by the kidneys, and when continued long may cause gastro-intestinal disturbances and diarrhœa.

Acute Thyroidism.—The symptoms produced by an overdose are as follows:—Rapid pulse, fever, headache, tendency to syncope, sickness, diarrhœa, restlessness, wandering pains, pruritus, and rarely delirium.

Chronic Thyroidism.—The symptoms are:—Loss of weight, muscular weakness and paresis, falling out of the hair, protrusion of the eyeballs, dilatation of the pupils with widening of the palpebral fissure, and finally death from malnutrition and asthenia. It will be noted that these symptoms closely resemble those of exophthalmic goitre.

THERAPEUTICS

The chief use of thyroid is in the treatment of myxœdema, which is a disease due to atrophy of the thyroid gland. In six weeks all symptoms will probably have disappeared, but to prevent recurrence the patient must take it twice a week for the rest of his life. In the same way it is invaluable in cretinism, which is a form of idiocy associated with dwarf-growth, due to congenital absence of the thyroid ($\frac{1}{320}$ to $\frac{1}{160}$ gr. thyroxine-sodium daily or on alternate days). Under this treatment, however, the bones of cretins have a strange tendency to bend. Thyroid has also proved of benefit in congenital imbecility, the insanity of the menopause and in menopausal headache, specially when associated with subnormal metabolic rate.

Paradoxical as it may appear thyroid is useful in goitre.

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In this condition the enlargement of the gland does not mean increased secretion, on the other hand the gland hypertrophies to compensate for the deficiency of the thyroxine. But it is useless in exophthalmic goitre. As thyroid hormone stimulates metabolism, it has been used in diverse conditions. For instance, remarkable results may be obtained in certain diseases of the skin, specially psoriasis, pityriasis rubra, ichthyosis, eczema, lupus, etc., whilst it sometimes causes a luxuriant growth of hair in alopecia. Administered with calcium it is of great value in chilblains. In obesity thyroid treatment has been found to be of value, but may do harm if used without proper precaution. Small doses of thyroid form a valuable remedy in obstinate constipation so often present in slight forms of hypothyroidism.

Thyroid deficiency is to a large extent responsible for a number of complaints and infections, and its administration has been advocated in acute and chronic arthritis, angina minor, acute tonsillitis, phlegmasia alba dolens, B. coli infection and chronic gout.

As a diuretic it is said to be valuable in reducing œdema of Bright's disease.

Cheron used it as a galactagogue, and in threatened abortion. Different observers have reported benefit from its use in infantile wasting, ununited fracture, and in assisting the development of backward children.

It is worthy of trial in children who fail to grow, in nocturnal enuresis, night terrors, and in those who suffer from relaxation of the ligaments causing knock knee, painful heel, flat foot or lordosis.

Prescribing hints.—Thyroid is best administered in the form of powder or as tablets. It is not as a rule a dangerous remedy, but when it is continued for a prolonged period it should be used with care, specially if the heart is affected. It is now realised that large doses are not required. A total daily dose of 6 grs. of the extract of fresh gland seldom needs to be exceeded, and it is wise to start with $\frac{1}{2}$ gr. doses three times a day. It should be noted that the extract of the desiccated gland is five times as strong as the fresh gland. Thyroxine can be given by the mouth, but it acts better when given intravenously.

Thyroxine-sodium is used under the same conditions as thyroid; and it should be used when thyroxine is ordered. The usual method is the intravenous route, and although it may be given by the mouth, its absorption by this route is uncertain. In every case the optimal dose should be first determined, the exact determination of which depends upon the basal metabolic rate. Ordinarily $\frac{1}{30}$ gr. daily in normal adult will produce symptoms of hyperthyroidism. Cases of myxœdema require from $\frac{1}{40}$ to $\frac{1}{30}$ gr. (0.0015 to 0.002 grm.) of thyroxine-sodium daily.

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Contra-indications.—Hypersecretion of the thyroid, and when there are toxic symptoms from hyperthyroidism. Sleeplessness, delirium, cerebral excitement and when the heart is rapid or irritable. In acute inflammatory condition of the skin and progressive loss of weight.

PARATHYROIDS

(Not official)

These glands are used in two forms.

1. **Desiccated Parathyroid Gland.**—*Dose*, 1/20 to 1/10 gr. or 0.003 to 0.006 grm. by mouth. Probably it is inert.

2. **Parathyroid Extract (liquid).** *Syn.*—*Parathormone* (Collip).—An acid solution containing the active principles of the gland. Its potency is estimated by the rise in calcium in the blood serum of dog. *Dose.*—20 to 40 units, *intramuscularly*. One unit is one-hundredth the amount required to raise the serum calcium of a dog weighing 20 Kg. by 5 mg. per 100 mils. 1 c.c. equals 20 units.

Pharmacology and Therapeutics

Parathyroids regulate the calcium metabolism, and increase the ionisable calcium content of the blood, and detoxicate certain metabolic poisons. Administration of parathormone (Collip) regulates the concentration of calcium in the body which has a sedative effect on the nervous system. The removal of the glands is followed by a condition known as tetany which is characterised by increased excitability of the motor nerves and certain parts of the central nervous system. Serum calcium falls from 10 to 8 or 6 mgrms. and the symptoms of tetany are due to the decrease of serum calcium. Administration of parathyroid raises the serum calcium, and since the absorption of calcium is not increased, nor its excretion diminished but rather increased (this occurs even after complete removal of the alimentary canal), the rise of serum calcium is attributed to the mobilisation of calcium from the soft tissues and bones. In fact after its use the bones become softer, and in growing animals and after fracture less calcium is deposited.

Apart from raising the calcium in the blood it increases the excretion of phosphorus in the urine. If however it is continued long in large doses, after the blood calcium has reached a certain height, the effect is reversed and the blood phosphorus rises again.

A single large dose has little effect, but repeated smaller doses show symptoms of hypercalcæmia by raising the calcium content of the serum to over 12 mg. or even up to 20 mgrms. per 100 c. c. These symptoms are vomiting, loss of appetite, diarrhœa, impaired circulation, dullness, drowsiness, general muscular flaccidity, and complete anuria. The general effect is vagotonia, with slow pulse, hyperæmia of the abdominal organs and increased gastric and intestinal movements. As this hyperæmia has a diuretic effect, its use has been advocated in **oliguria** and **anuria** associated with glomerulo-nephritis, specially when the blood calcium is lowered. In **tetany** the calcium content of the blood is reduced, and the administration of the extract increases the calcium and relieves the symptoms more effectively than the use of calcium salts alone. It has also been used in the treatment of **paralysis agitans, eclampsia, epilepsy** and **chorea**, in doses of 1/10 gr. daily. Its use has been advocated in **sprue** with simultaneous use of calcium.

It has been extolled by Grove and Vines in the treatment of **varicose ulcers** of the leg and also in **gastric** and **duodenal ulcers**. They found a deficiency of ionic calcium in the blood which was restored to normal by the use of parathyroid accompanied by the healing of the local lesion and general improvement of the health.

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They have shown that the administration of the parathyroid increases the calcium content of the blood when deficient, and this it does even when the use of the calcium by the mouth or intramuscularly has very little effect. They further aver that the parathyroid improves septic conditions, and that deficiency of calcium is an index of the absorption of the toxins.

Except in cases where there is distinct deficiency of blood calcium, *i.e.*, below 10 mg. per 100 c. c. its use in other conditions is at best a speculative one. As it mobilises the calcium from other tissues, mainly the bones and muscles to the blood, its use in rickets is contra-indicated if not dangerous.

The best results are obtained when the extract is administered subcutaneously as in the treatment of tetany. It has been given by the mouth but the results have not been very satisfactory, and it is doubtful whether administered by the mouth it raises the calcium content of the blood. The administration of the extract should be controlled by determination of the calcium content of the blood to avoid hypercalcæmia.

INSULINUM

Insulin

Source.—A preparation containing the specific antidiabetic principle of the mammalian pancreas. Prepared in the form of powder or solution. May be obtained in solution by dissolving the necessary quantity of dry powder in distilled water acidified to a reaction between the limits of *p*H 3 and *p*H 4, so that the solution contains 20 units per mil. Some antiseptic is added to prevent growth of bacteria.

Characters.—Colourless liquid, free from turbidity and from matter which deposits on standing.

May be obtained in tablet form which must be readily and completely soluble in water.

B. P. Dose.—5 to 100 units (subcutaneously).

Three units of insulin is the amount in c.c. which on subcutaneous injection into a normal rabbit weighing 2 kg. reduces its blood-sugar from the normal of 0.15 p.c. to 0.045 p.c. within 2 hours. At this point the rabbit develops coma and convulsion.

Action and Uses

Since the experiments of Von Mering and Minkowski, who demonstrated the relationship of the pancreas to carbohydrate metabolism, attempts have been made to extract from the pancreas the active substance responsible for the utilisation of glucose, but they were all unsuccessful, till in 1921 Banting, Best and McLeod of the Toronto University prepared a pancreatic extract which was found to give the most successful results in diabetes, and to which the name of insulin was given by Schafer.

Insulin is the active principle of the pancreas, which is produced in the islets of Langerhans, and which being constantly secreted into the blood plays an important part in the metabolism of carbohydrate.

Removal of pancreas in animals is followed by a rise of blood-sugar above normal and appearance of sugar in the form of dextrose in the urine. Since the glycosuria appears

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even in the absence of any carbohydrate food from conversion of other substances in the body into dextrose, the body gets depleted of sugar and the animal loses weight. There is not only failure to utilise sugar, but the metabolism of fats is also affected, and as a result of incomplete oxidation of fats there accumulates in the body *aceto-acetic acid* and *β-hydroxybutyric acid* which are excreted in the urine. An injection of insulin controls carbohydrate metabolism, and will reduce blood-sugar of healthy animals from the normal of 0.12 p.c. This effect takes place normally within an hour of its administration and is maintained several hours, but rarely over ten hours. The extent of the fall depends upon the amount given, and an overdose produces symptoms of hypoglycæmia. It helps the tissues to metabolise sugar and enables the liver and muscles to store glycogen. Since injection of insulin in depancreatised dog, which is also given sugar, increases the respiratory quotient, it is evident that sugar is being oxidised, and it has therefore been suggested that insulin supplies the missing link, and by the control it exerts on the glycogenolytic ferment permits of sugar being converted into a form suitable for oxidation. Insulin therefore has been extolled as a most valuable drug in the treatment of **diabetes**. Under its use there is a marked reduction of the blood-sugar which remains at the normal level while the glycosuria disappears altogether. Along with the disappearance of sugar from the urine the ketone bodies usually disappear from the urine and blood within twenty-four to forty-eight hours, showing that fats are more efficiently dealt with. The carbohydrates are utilised more freely with a rise of respiratory quotient. In fact patients under insulin treatment show clear signs of improvement, and the cardinal symptoms of diabetes are relieved. But the best results are obtained in cases of threatened or actual **diabetic coma**, when larger doses (40 to 60 units) are given preferably by the intravenous route and as much as 200 units may be given in 24 hours. Since acidosis is the result of imperfect combustion of fats, it is necessary that fats should be withdrawn and carbohydrates in the shape of glucose administered. Other measures such as rectal injection of 3 p.c. solution of sodium bicarbonate should be adopted. To be successful the treatment must be started early. A case in which the coma has existed for more than twenty hours without any improvement is hardly likely to recover under insulin.

It has been used with success in the treatment of furunculosis not only when associated with diabetes but also in cases where there is no sugar in the urine but the blood-sugar content is high. Carbuncles in diabetics heal more rapidly under insulin treatment. Conditions depending on hyperglycæmia, *e.g.*, neuralgia, pruritus, balanitis, etc., disappear

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under insulin. It is also of great value in **acidosis** and **ketosis** of non-diabetic origin. Thus hyperemesis gravidarum is successfully treated with injection of insulin and glucose. Similarly cyclical vomiting of children is equally benefited by insulin and glucose. Its use has been suggested in exophthalmic goitre, it improves the goitre and exophthalmos and reduces the basal metabolic rate. As a prophylactic against acidosis prior to surgical operations and anæsthesia, specially in the diabetic, its value is undisputed.

Its use has recently been suggested in **malnutrition**, it increases the weight in patients with intact carbohydrate metabolism, improves the subcutaneous tissue and gives a healthier appearance to the skin. The method is to give 10 units three times before each meal the first day, and increasing by 5 units daily up to 20 to 30 units. It has been suggested that the good effects are due to (1) an increased demand for food; (2) an improvement in the nutritive condition, causing an increased desire to eat; and (3) training of the insulin-producing organs by carbohydrate administration to produce more insulin.

Methods of Administration.—Insulin has no action when given by the mouth or per rectum, as it is rapidly destroyed by the digestive enzymes. Within certain limits perilingual administration may be successful, but cannot be regarded as a substitute for injection, although Mukherjee* claims that the phosphotungstate precipitate is active by the mouth. It is doubtful, however, whether its absorption is sufficient to replace subcutaneous injection, and in all cases where immediate effect is necessary the subcutaneous route should be the route of choice. Two perilingual tablets can only be given daily which means ten units of insulin. It should always be given subcutaneously, or in urgent cases, intravenously. One unit of insulin will metabolise 2 grms. of carbohydrate and 30 to 40 units a day is the normal dose in severe cases. The usual dose for an adult is 10 units, repeated twice daily, and should be given a quarter to half an hour before a meal so that it can exert its effects on the glucose which reaches the blood from the meal. This precaution will prevent the risk of hypoglycæmia. The dose of insulin depends upon

(1) the severity of the case;
(2) weight, a heavier individual requires a larger dose;
(3) amount of intake of food; and
(4) septic or other complications.

Whenever possible the treatment should be controlled by blood-sugar estimation. If this is not practicable the dose of 20 units should not be exceeded. During insulin treatment the patient should not be allowed to fast too long after the injection. When the insulin requirement exceeds 40 to 50

* Journal of Physiology, 1935, p. 362

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units daily, it is better to divide it into two or three doses. The single dose method is unsatisfactory when the daily requirement exceeds ten units.

Before adopting treatment always make sure that the case is really one of diabetes. It is dangerous to treat cases like renal glycosuria, where the blood-sugar is already low. It is desirable before adopting insulin treatment to try the effect of dieting, and when the patient is doing fairly well on diet insulin should not be given. If however the blood-sugar still remains high, the additional carbohydrate requires to be metabolised by the administration of insulin. Since 1 unit will ensure metabolism of 2 grm. of sugar, the daily dose should be in proportion of half to the daily amount excreted in grammes, and should be given in 2 to 3 divided doses half an hour before meals followed by some sugar.

Result of overdosage.—A dose of insulin which will lower blood-sugar in rabbits to 0.045 p.c. or less causes increased reflexes, rapid and shallow respiration, clonic convulsion, coma and death. These symptoms are arrested by the administration of glucose. In man the symptoms of hypoglycæmia are observed when insulin is given in very large doses, or when the supplement to the diet is not given in the proper time relation. The severity of the symptoms depends upon the fall of blood-sugar. When the blood-sugar content is 0.07 p.c. the patient only experiences a sense of uneasiness and nervousness with a feeling of impending danger. When it is below 0.06 p.c. there is weakness, nervousness, dizziness, disturbances of sight and profuse perspiration. If the sugar is reduced still further, *i.e.* 0.04-0.055 p.c., there is aphasia, disorientation, mental confusion, loss of reflexes, and perhaps coma and death. The symptoms are possibly due to defective supply of glucose to the nerve cells of the brain, and are rapidly removed by the administration of some carbohydrate. Insulin exerts its maximum effects about four to five hours after injection, therefore the symptoms of overdosage appears at this time. These symptoms are induced or aggravated by exercise ; and all patients should be warned of this possibility and should be advised to keep some sugar preparation for an emergency. An ounce of glucose or other sugar solution may be given by the mouth. If the patient is unconscious, or the symptoms have lasted long, it is necessary that glucose should be given by intravenous injection, 5 to 20 grms. being given in 50 to 100 c.c. of water. Adrenaline is often useful but is not so certain as glucose as its effect depends upon the availability of glycogen in the liver, which may be present in very small amount, so that even if adrenaline is given glucose should also be administered.

Conclusion.—Insulin is not a cure for diabetes, but it is a valuable aid to the physician specially in cases of diabetic

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coma. It has helped diabetic patients to undergo surgical operations without any danger. The only drawback is that its effects do not last long, and it has to be used for an indefinite period, at least in some severe cases, while in others it fails to make the urine sugar-free.

The importance of distinguishing diabetic coma from insulin coma is obvious, and Graham gives the following rules for distinguishing them :—*

	Insulin Coma	Diabetic Coma
1.	Skin usually very white, may be normal in colour	Skin usually flushed
2.	No smell of acetone in breath	Breath smells of acetone
3.	Respiration shallow	Respiration deep (abdominal respiration is characteristic)
4.	Urine usually sugar-free, except when bladder not emptied for some hours or blood-sugar was above 200 mgrm. per 100 c.c.	Always contains large amount of sugar
5.	Eyeball tension normal or raised	Eyeball tension much lower
6.	Urine need not contain aceto-acetic acid	Urine always contains large amounts of aceto-acetic acid
7.	Blood-sugar below 70 mgrm. per 100 c.c., may be below 40 mgrm.	Blood-sugar over 200 mgrm. per 100 c.c. may be even 500-800 mgrm.

GUANIDINE

(Not official)

Guanidine or *Imido-urea* is found in certain plants and can also be obtained from certain proteins. It resembles physostigmine in action, and at one time was considered responsible for the causation of idiopathic tetany of children and related to parathyroid metabolism. It has however the property of reducing blood-sugar and producing hypoglycæmia. Subsequently Frank and others introduced Synthalin and Synthalin B, both guanidine derivatives, with properties similar to those of insulin, but without its toxic effects and which unlike insulin are effective when administered by the mouth. How synthalin acts is not known, but it is possible that it acts either by lowering the cellular threshold for glucose-insulin metabolism, or more probably, by depressing glycogenolysis, thereby increasing the secretion of endogenous insulin. It is extolled by some but so far the results have not been uniform.

Some patients show intolerance to synthalin. The symptoms are vague dyspepsia, feeling of weight in the upper abdomen, flatulence and feeling of distension, constipation or often looseness with colicky pain, loss of weight and general malaise and languor. These symptoms are rare when a high carbohydrate and a low fat diet is given. †

Synthalin.—Decamethylene diguanidine bihydrochloride. *Dose.*—1/6 gr. or 0.01 grm.

Synthalin B.—Dodecamethylene diguanidine dihydrochloride. *Dose.*—1/12 gr. or 0.005 grm.

Action of other Hormones

The exact manner in which the different animal extracts or their active chemical substances produce their characteristic effects is still

* G. Graham, *Medical Press and Circular*, 1934, Symposium No. 1.

† Todd, Brinckman and Sansom, *The Practitioner*, May 1932.

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a matter of speculation. But it is generally believed that some act by influencing the cell metabolism, while others through the sympathetic or parasympathetic systems. There can be no doubt that thyroid affects metabolism by acting on the different cells of the body, while the action of pituitary is specific and affects only certain types of cells. Adrenaline on the other hand produces its effects through the medium of the autonomic nervous system.

The different endocrine organs are used therapeutically for the following objects:—

1. *Substitution Therapy.*—This it does by supplying the missing hormone the loss of which is known, *e.g.*, the use of thyroid in cretinism and insulin in diabetes mellitus.

2. *Supplemental Therapy.*—This is done by supplying a presumed deficiency, due either to an increased demand or decreased output. It is possible that in some instances the improvement is due to stimulation of the analogous organs to increased activity, when it is known as *homostimulation.*

3. *Physiological Therapy.*—In this advantage is taken of our knowledge of pharmacology of certain gland extracts, and they are used to produce definite effects either through the sympathetic nervous system, or directly on the tissues concerned, and not through any alteration in the normal hormone product, *e.g.*, adrenaline.

THE THYROID GLAND

There are two classes of disease associated with abnormality of the thyroid gland:—

1. Those in which there is an absence of the internal secretion.
2. Those in which the internal secretion is either abnormal or excessive.

1. The treatment by means of thyroid extract has been fully dealt with *(see* page 576).

2. Under this head is **exophthalmic goitre or Graves' disease.** Numerous methods have been devised with the object of neutralising excessive and abnormal secretion to which the unpleasant symptoms of the disease are believed to be due.

The chief of these are the following:—

1. The use of the milk of thyroidectomised goats.
2. „ the serum of thyroidectomised sheep.
3. „ thyrolytic serum.

1. The Milk of Thyroidectomised Goat

The theory of this remedy is that when the goat has been deprived of its thyroid its milk will contain an excess of the toxin which is normally destroyed by the thyroid, and hence will tend to neutralise excessive thyroid activity. This method of treatment has obvious disadvantages and it has been given up in favour of the next method, which depends upon similar principles and is easier to carry out.

2. The Serum of Thyroidectomised Sheep

This is obtainable in two forms:—

1. Moebius's Serum, or Antithyroidin.
2. Thyroidectin.

(1) *Moebius's Serum.*—This is blood serum obtained from rams six weeks after extirpation of the thyroid, to which 0.5 p.c. phenol has been added as a preservative. It is said to keep indefinitely and is therefore more generally useful than the milk, besides which it probably contains a larger proportion of toxins. The patient becomes quiet, sleeps better and puts on weight, whilst both the exophthalmos and the swelling subside. The amount of serum to be used varies in different cases and the amount given cannot be increased indefinitely; otherwise there is danger of producing

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symptoms of athyroidism, namely a mild type of myxœdema with headache, apathy and mental stupidity.

Administration.—Until recently it was given by the mouth, either in solution or in tablets. But the intramuscular injection appears to be the best.

Dose.—*Intramuscular*, ordinarily about twenty injections of 1 c.c. each is required, but in severe cases as many as thirty, once a day for the first fortnight and later one every two or three days only.

By mouth, the serum 10 drops three times a day, increasing every day by 5 drops till 30 drops are given per dose, and then to reduce it the same way. After 50 c.c. in all have been given, the treatment should be stopped for a week, and can be resumed again for a short period with 10 to 20 drops three times a day.

(2) *Thyroidectin.*—This is a brown powder prepared by inspissating the serum of thyroidectomised animals. Its use is similar to that of Moebius's serum. *Dose.*—5 grs. in capsule.

3. Thyrolytic Serum

Beebe has prepared an antithyroid serum, which not only contains a specific cytotoxin, but also has the power of neutralising the thyroid secretion. He accomplished this by isolating the neucleo-proteins and the thyroglobulin of two glands removed from patients with exophthalmic goitre and injecting these into rabbits. This serum, being made from human organs is capable of doing great harm to man and must therefore be used very cautiously and in small doses slowly, not more than 1 c.c. for injection.

THE THYMUS

Persistent enlargement of the gland in exophthalmic goitre led to the belief that this enlargement was conservative, and preparations of thymus gland were used in the treatment of this disease with very doubtful results. On the other hand some hold that its persistence is the cause of Graves' disease. It has also been used in a variety of conditions including nutritional disorders in children, but there is little positive evidence of its value. Given in tablets, 2 to 4 grs.

MUSCLE EXTRACT

Within recent years extract of mammalian tissue has been used in the treatment of cardiac and circulatory disturbances. A preparation called **Lacarnol** (extract of heart muscle) has been placed on the market and is claimed that it has a specific action in dilating the vessels, specially coronary arteries. The indications for its administration are cardiac failure, arrhythmia, angina pectoris, intermittent claudication, and (occasionally) hypertension. There is evidence that muscular exertion liberates antispasmodic and vaso-dilator substances, which sometimes prevent anginal attacks or intermittent claudication. Muscle extract is specially useful in spasmodic angina; attacks due to cardiac dilatation or coronary thrombosis are seldom if ever relieved. Apart from these vaso-dilator and antispasmodic effects, muscle extracts appear to have a cardiotonic and regulating action, relieving decompensation and arrhythmia. The action sometimes resembles digitalis, in fact the effect is very definite when both are given in combination. It is still in its experimental stage.

It may be used both *hypodermically* and by *mouth*. The *dose* of Lacarnol is 10 to 25 drops, once or thrice daily, or 1 c.c. hypodermically. Another preparation is **Sarcolan**, dose 1 c.c. hypodermically.

A crystalline substance 'adenosine' obtained from muscle extracts has a very powerful vaso-dilator action on the coronary arteries of the guinea pig.*

* *British Medical Journal, Epitome*, July, 8, 1932.

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THE BONE MARROW

This is the bone marrow obtained from ribs and flat bones. Red bone marrow contains largely (about 90 p.c.) of fat and in new born animals one-third of the fat is lecithin; it also contains iron in organic combination.

It is supposed to stimulate the formation of red blood corpuscles. This action is probably due to the presence of iron and lecithin. It is used as a remedy in **pernicious anæmia, chlorosis, scurvy, purpura, hæmophilia, debility, leucocythæmia, lymphadenoma.** Owing to the presence of active cholesterol, fresh red bone marrow has a distinct **antirachitic** value.

It can be administered in the fresh state, but it is difficult to prepare, and is better as a rule to use one of the various preparations that are on the market, *viz.*—1. **Bone Marrow Tabloids.**—3 grs. each; **Virol,** and **Marrubin,** a glycerin extract of ox-bone marrow, as a palatable substitute for cod-liver oil. *Dose.*—1 to 2 drs.

THE SPLEEN

Hormonal (extract of spleen) injected subcutaneously increases intestinal peristalsis and acts as a purgative (page 334). Its effects are however uncertain, and sometimes produces dangerous symptoms and even fatal effects. It was believed that the purgative effect was due to the presence of a special hormone, but since other organ extracts produce similar effects, it is possibly due to the presence of histamine, choline or other products of tissue katabolism. Usual dose is 15 to 20 c.c. Two forms are issued, one for intramuscular injection, the other for intravenous injection. Castor oil one ounce should be given simultaneously.

An extract of pig's spleen has been used with success in the treatment of **tuberculosis.** The usual dose is 5 c.c. for adults *intramuscularly* into the thigh, or *subcutaneously,* twice a day. It has been credited to stimulate calcium metabolism and to possess hæmostatic properties, and has been used in menorrhagia and anæmia.

GROUP XXIII

DRUGS ACTING ON THE BLOOD

Changes in the blood both in quality and quantity may occur necessitating the use of remedial measures. The most important change occurs with regard to the red blood cells. They may be diminished in number, or there may be deficiency of hæmoglobin, and since the oxygen-carrying power of the blood depends upon the amount of hæmoglobin in the corpuscle, deficiency of hæmoglobin, *i.e.*, anæmia, demands early treatment. Iron is its chief constituent and the body contains about 3 grm., and about two-third of the iron in the body exists in the form of hæmoglobin, the rest is stored in the liver, spleen and other tissues by the reticulo-endothelial cells.

Normally the red blood corpuscles have an average life of about three weeks, hence they require constant renewal to maintain the red blood cells at the normal level. These are manufactured in the red bone marrow. Drugs which increase the number of red blood corpuscles are known as **hæmatinics.**

Diminution of the red blood supply to the blood-forming

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organs acts as a stimulus and causes regeneration of the red blood cells. On the basis of this theory venesection has been done in chlorosis to stimulate the inactive bone marrow.

Hæmatinics have no effect in increasing the amount of iron in healthy blood. They act only when either the hæmoglobin or the number of red corpuscles are deficient. The red blood corpuscles are manufactured in the red bone marrow. Arsenic causes hyperæmia of red bone marrow, and liver extract causes increased formation of red blood cells. Iron and its salts, and stomach extract are also valuable hæmatinics.

In order that the student may understand the rational treatment of anæmia it is necessary that he should have a clear conception of the underlying factors which produce the condition.

Recent studies have brought to light the different factors which control the formation of the red blood cells in the bone marrow. A special hæmatinic (anti-anæmic) principle, is necessary for the development of the megaloblast to the erythroblast stage, and the relationship of iron in the transformation of the erythroblast into a mature erythrocyte has long been recognised, while recently the part played by copper, thyroxine and vitamin C is being mooted.

Anæmia has been classified broadly into the following two groups :—

A. *Macrocytic Hyperchromic Anæmia.*—Pernicious anæmia is the typical example of this variety, and is characterised by a reduction in the number of red cells, which become abnormal in shape and size (tend to become larger), but the hæmoglobin is correspondingly less diminished so that there is a high colour index (hyperchromic). The blood maturing function of the red bone marrow is disturbed from the absence of the maturing principle which is stored in the liver. This principle is formed in the stomach by the interaction of an agent present in the gastric juice (*intrinsic factor* or *hæmatinic principle* of Castle), with another substance formed from the protein as a result of gastric digestion (*extrinsic factor*). It follows therefore that any breakdown in the above chain will cause macrocytic anæmia as a result of the failure of megaloblastic maturation.

(*a*) The breakdown may be in the intrinsic factor due to deficient secretion, possibly responsible for Addisonian pernicious anæmia.

(*b*) The breakdown may be in the extrinsic factor. Malnutrition (absence of high grade proteins and fresh vegetables) specially in the tropics is an important factor in the production of megalocytic hyperchromic anæmia. The anæmia of pregnancy is believed to be due to the absence of this factor and is successfully treated with proper diet and autolysed yeast.

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(c) Both factors may be present, but owing to the abnormal state of the intestinal canal it may fail to absorb and utilise the hæmatinic principle. This possibly occurs in the presence of intestinal parasites or when there is impermeability of the intestinal mucosa. Faulty absorption of the hæmatinic principle is perhaps the cause of the failure to response to liver adiminstered by the mouth, though these cases improve when administered by intramuscular injection.

According to Castle (*Lancet*, 1932, Vol. 1) all the above factors are at work in tropical sprue.

(*d*) Faulty storage of the hæmatinic principle (P. A. Factor). It is possible that associated with this fault there is also mineral deficiency, and these cases improve when iron is given with liver. In cases of megalocytic hyperchromic anæmia associated with intestinal lesion this dual deficiency may be present.

B. *Microcytic Hypochromic Anæmia.*—This is primarily due to iron deficiency either in the diet, *e.g.*, nutritional anæmia of infants; or when absorption of iron is defective consequent on achlorhydria (chlorosis falls under this group), or when there is increased demand for iron, as in pregnancy, menorrhagia, etc.

A mild form of anæmia of this variety may occur in thyroid deficiency, which is cured by a course of thyroid. Iron and copper, also vitamin C are necessary for the transformation of erythroblats to erythrocytes.

Anæmia after hæmorrhage is also of microcytic type which responds to iron therapy, so also anæmia due to some toxins (toxic anæmia), *e.g.* anæmia of malaria, and other infectious diseases.

The anæmia of pregnancy may be of the microcytic type from deficiency of iron in the diet, or from defect in the absorption of iron from disturbances in the stomach and intestine, or from excessive drainage of iron. These improve under iron. But the intrinsic factor may also be involved leading to the pernicious type of anæmia.

Aplastic anæmia is a condition where the activity of the bone marrow is entirely suspended, and generally follows the use of certain drugs, *viz.* lead, mercury, benzene, etc. Arsenic causes some hyperæmia of the red bone marrow and is often used, although its exact mode of action is not known. Repeated transfusion of blood has been recommended in the hope that the bone marrow may regain its hæmopoietic functions.

White blood corpuscles.—These corpuscles are migratory in their habits, and in case of inflammation they wander through the capillary walls. Salicylic acid, quinine and other cinchona alkaloids arrest their movements in very dilute solutions, while in concentrated solutions they are destroyed. They are also destroyed by X-rays and benzol.

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Counter-irritants at first cause leucopænia followed by leucocytosis. Salts of calcium increase their activity and the phagocytic power in a definite manner. White blood corpuscles are increased by (*a*) pilocarpine, which causes contraction of smooth muscles of the spleen and lymphatic glands; (*b*) bitters and volatile oils, which irritate the mucous membrane of the intestine; (*c*) radium, which causes irritation of the blood-forming organs; and (*d*) injection of a foreign protein like milk.

Coagulation of blood.—One of the most important functions of the blood is its power to coagulate shortly after it leaves the blood vessels. The essential part of the clot is fibrin, an insoluble protein compound not normally present in the circulating blood, but formed from fibrinogen present in the plasma by the action of thrombin. In the circulating blood thrombin exists as inactive prothrombin which is changed to thrombin by the addition of tissue extracts, which contain lipoid thromboplastic substances (thromboplastin, thrombokinase, cephaline); by the presence of minute amounts of ionised calcium salts; and possibly by a similar substance liberated from the disintegration of blood platelets after hæmorrhage. Coagulation of blood can be increased therapeutically by the administration of calcium; transfusion of whole blood not only to replace the lost blood but also to supply any elements that may be lacking; normal serum, which contains some thrombin and prothrombin; coagulen, a preparation from blood platelets, which yields both thrombin, and thromboplastin; and cephaline, a lipoid obtained from ox brain.

Coagulating power of the blood is diminished by inactivating the calcium by citrates or oxalates. Leech extract or hirudin contains an anti-coagulant substance which prevents clotting. These measures are hardly used in therapeutics but are of value in animal experiments.

The plasma.—The chief function of the plasma is to carry nutrient materials, hormones and drugs to the different tissues, and the excretory products to the kidneys. The plasma proteins help conversion of fibrinogen into fibrin when blood is shed. By exerting an osmotic pressure they tend to retain fluid in the capillaries and help to maintain the blood volume, regulate interchange between the blood and the tissue spaces and influence the filtration in the glomeruli in the kidney. The plasma contains and can develop immune bodies, *e.g.* agglutinins, precipitins, opsonins, etc., and obviously is of great value both in health and disease.

Reaction of the blood.—The normal reaction of the blood is almost neutral or weakly alkaline with a *p*H of 7.3 to 7.5, and life is incompatible when the *p*H of blood is below 7.0 or above 7.8. The maintenance of the *p*H at its normal level

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in the blood and tissues is regulated by the carbonates and alkaline phosphates which form the alkaline reserve, and by the carbonic acid, the phosphates and proteins which form the acid reserve. The body is protected from the harmful effects due to variations of reaction not only by the buffer action of these salts, but also by the lungs, kidneys, and probably the intestine. The lungs get rid of the excess of CO_2 and the volatile acids (oxybutyric acid series) and the kidneys by increased excretion of fixed acids, and by increased ammonia formation.

Acidosis.—By acidosis is meant a condition in which the reaction of the blood is less alkaline than normal, and the blood is taken as an index of the reaction of the tissues generally. This may happen when the alkaline reserve of the body is depleted. Acids are always being produced in the body as a result of katabolic activity, but provision is made for their neutralisation and excretion through the buffer action of the blood and tissues, and the excretory functions of the lungs and the kidneys. So long as this production of acid remains within normal limits and the organs concerned in its removal are functionating, there is no evidence of their disturbance. Of the acids, phosphoric, sulphuric and lactic and the other organic acids are neutralised as soon as they are formed, so that they are always present in the blood and tissue fluids as salts. CO_2 on the other hand is not completely neutralised and is found in the blood as a free acid in solution. In herbivorous animals owing to their food being rich in potassium and sodium, the acids are eliminated as salts of fixed alkalies, and the blood becomes depleted of its store of fixed alkalies when a large amount is lost. In carnivorous animals and in man there is no such loss as the acids are excreted in combination with ammonia, because their food contains little fixed alkalies and the acid products of metabolism are neutralised by ammonia liberated by the tissues thus protecting the fixed alkalies. In acid poisoning therefore ammonia salts excreted by the urine are increased. This protection is normally present but may fail when there is increased production of acids, as in diabetes due to defective oxidation of the products of fat metabolism resulting in the accumulation in the body of substances known as ketone bodies, *viz.* acetone, aceto-acetic acid and β-hydroxybutyric acid (ketosis); in nephritis from diminished excretion of acid; after exercise, and in arsenic and phosphorus poisoning from excessive production of lactic acid; by the use of large doses of ammonium and calcium chloride; or by adding to the body one of its acid elements, *viz.* chlorine. Interference with the excretion of CO_2 by the lungs so that it may combine with water to form carbonic acid (H_2CO_3) which dissociates to yield H-ion, also increases the hydrogen-ion concentration.

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of the blood. Minor degree of acidosis is also present after fasting specially with a low carbohydrate diet, in chloroform narcosis, etc. The term ketonæmia or acetonæmia signifies the presence of ketone bodies in the blood above 3.0 mgm. per cent., and ketonuria or acetonuria their presence in the urine.

Alkalosis.—By this is meant a condition in which the blood is more alkaline than normal. Owing to the ease with which the body can accumulate acids, alkalosis is not so common as acidosis, but a mechanism exists to prevent the reaction of the blood and tissues from becoming too alkaline. It occurs clinically in persistent vomiting, high intestinal obstruction and pyloric obstruction due to loss of hydrochloric acid, so that there is uncompensated acid deficit and accumulation of bicarbonates; by forced breathing, thereby eliminating an excess of CO_2 from the alveolar air thus lowering the CO_2 tension in the arterial blood; by calcium deficiency, as after parathyroidectomy or tetany; and by the use of large doses of alkalies.

Toxicology of blood.—Certain drugs like arsenious acid, phosphorus, iodine, sulphur, oil of turpentine and hydrocyanic acid reduce hæmoglobin in poisonous doses. Alcohol and quinine bind oxygen so firmly to hæmoglobin that its oxygenating power is impaired. Phenazone, phenacetin and acetanilide, potassium chlorate and pyrogallol convert a portion of hæmoglobin into methæmoglobin in poisonous doses.

Hæmolysis or destruction of red blood cells also occurs when the osmotic pressure of the surrounding fluid becomes lower than the corpuscles, as happens when the blood is greatly diluted with pure water. Conversely hæmolysis may occur if the blood corpuscles have a higher osmotic tension than normal plasma, as happens when concentrated salt solution or pure glycerin is injected into the tissue. Besides the osmotic changes, saponins, ether, chloroform in sufficient concentration act as hæmolytics. In practical therapeutics this is unimportant as saponins do not enter the blood unchanged from the intestine, and the narcotics do not reach the blood in sufficient concentration to produce any hæmolytic effect.

Class A : **Drugs used in Macrocytic Hyperchromic Anæmia**

EXTRACTUM HEPATIS SICCUM

Dry Extract of Liver

Syn.—Extract of Liver.

Source.—It is a selected fraction of an alcoholic extract of ox or sheep liver, and contains the specific principle, which increases the number of red corpuscles in the blood of persons suffering from pernicious anæmia.

Characters.—A light, brown, very hygroscopic powder; odour, faintly meatlike; taste, saltish and meatlike. *Soluble* in water, almost insoluble in alcohol (90 p.c.).

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B.P. Dose.—The quantity equivalent to 225 grm. or about half a pound of fresh liver.

Official Preparation

1. **Extractum Hepatis Liquidum.**—A selected fraction of an alcoholic extract of ox or sheep liver, dissolved in a mixture of glycerin, alcohol and distilled water. Contains the specific principle which increases the number of red blood corpuscles in pernicious anæmia. 1 oz. is equivalent of 8 oz. of fresh liver. **B.P. Dose.—30 mils. or 1 oz.**

Pharmacology and Therapeutics of Liver

Liver is extensively used in the treatment of pernicious anæmia. How it acts is not clearly understood, although it is possible that it supplies a substance which acting on the bone marrow brings about maturation of the red cells and which substance is missing or not available in this disease. In pernicious anæmia the hydrochloric acid is deficient and there is gastro-intestinal stasis, and that constant absorption of toxins prevents the liver from manufacturing the secretion supposed to help the maturation of megaloblasts. The anti-anæmic factor is produced in the stomach (*see* p. 315) from the interaction of a gastric ferment (intrinsic factor of Castle or hæmopoietin of Wilkinson), and an extrinsic factor formed by the protein as the result of gastric digestion. This product which is thermolabile is converted in the liver into a thermostable substance possibly in association with vitamin B, and is the true anti-anæmic factor.

The value of liver treatment is well established in (*a*) *tropical megalocytic hyperchromic anæmia*; (*b*) *Addisonian pernicious anæmia*; (*c*) *tropical sprue*; (*d*) *pernicious anæmia of pregnancy*; and (*e*) *megalocytic hyperchromic anæmia* associated with infestation of the intestine with some parasites, lesions of the gastro-intestinal tract, and disease of the liver. All these anæmias have certain morphological features in common, they are megalocytic and hyperchromic, and the bone marrow shows hyperplasia of the more primitive red cells. Minot and Murphy claim that patients having a count of red blood cells below 2,700,000 per cm. showed marked improvement after a diet of liver within one month. The blood picture of a patient showing 1,509,000 red blood cells before treatment went up to 3,360, 000 after one month, 4,250,000 and 4,650,000 after two months and four to six months respectively. Along with this improvement the general condition improves, the appetite returns, and weakness and depression disappear rapidly.

Liver has also been used to counteract certain unpleasant toxic effects which follow the administration of arsenic and bismuth, and it has been used in the dermatitis which follows the use of these drugs.

Prolonged administration of liver has been advocated in hæmophilia on the theory that it plays an important part in

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the production of those factors essential for coagulation of blood.

The administration of either fresh liver in doses of 100 grms. daily, or of liver extract (prepared by extracting with water at 35°C.) in 1 grm. doses, is recommended in the treatment of hepatic cirrhosis. It is claimed that it causes cessation of hæmorrhages and disappearance of hæmorrhoids and ascites.

Owing to the presence of a depressor principle, hepatic extract is said to lower blood-pressure by facilitating detoxication, and has been recommended in the treatment of arterio-sclerosis. The blood-pressure may fall temporarily owing to the presence of choline and histamine in the extract but not to any specific liver secretion. It has however repeatedly failed in the writer's hands when given in carefully selected cases both by the mouth and subcutaneously.

Liver is rich in vitamins, specially vitamin B.

Mode of administration.—For therapeutic purposes the liver of sheep, goat, oxen and calf are used, and may be given either in the dry form or as liquid extract, or cooked according to the taste and choice of the patient, but prolonged cooking should be avoided. Half a pound daily of cooked liver is sufficient to bring about a prompt response. One ounce of the liquid extract is equivalent to half a pound of the fresh liver. But there are obvious disadvantages of using daily large amounts of liver which the patient very soon begins to dislike or may be unable to tolerate owing to gastro-intestinal disturbance. To obviate these difficulties liver extract may be used either by the mouth or as intramuscular or intravenous injections. Ordinarily administration by the mouth is sufficient, but in cases of severe relapse or when rapid action is necessary, the intramuscular or the intravenous route may be adopted. Although the greatest benefit is derived from intravenous method of administration, the general use by this route has potential dangers, and the routine method should be by the mouth, or if necessary by intramuscular injection. The dose for intravenous use is 0.1 grm. per kilo of body weight dissolved in physiological salt solution, so that 20 c.c. should contain 1 grm. of liver. It is necessary that the active principle should be sufficiently purified to avoid any allergic phenomena or a fall of blood-pressure. Preparations for intramuscular or intravenous use are many and these are given once, twice or oftener a week as may be necessary.

Untoward effects.—Injection of liver extract is sometimes followed by certain reactions. They are classified as follows: pain and local reaction; acute fall of blood-pressure; and allergic manifestations such as urticaria, collapse, dyspnœa, and generalised erythema.

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VENTRICULUS DESICCATUS, B.P.C.

Desiccated Stomach. (Not official)

Syn.—Ventriculin ; Gaster Sicca.

Source.—Whole desiccated stomach of hog, sheep or oxen, defatted with petroleum benzene. No taste, and very little odour.

Dose.—¼ to 1 oz. or 8 to 30 grm.

Action and Uses

Castle and Townsend have shown that healthy stomach secretes a substance which when absorbed acts upon the bone marrow in such a way as to bring about maturation of the red blood cells. This is supposed to be stored either in the liver, kidneys or other organs. This substance is formed by the action of an intrinsic factor present in normal gastric juice upon an extrinsic factor present in the food digested. It is assumed that patients suffering from pernicious anæmia do not secrete this antianæmic substance, and the failure of the red bone marrow cells to mature in this disease is associated with the inability of the patient to develop the blood-maturing substance. Subsequently Isaac and Sturgis have shown that desiccated and defatted chopped up gastric tissue contains in abundance this active substance. Desiccated stomach therefore has been used in the treatment of macrocytic hyperchromic anæmias, *i.e.*, pernicious anæmia, hæmolytic anæmias associated with pregnancy and sprue, and other macrocytic anæmias, and cases intolerant to liver. The usual dose is 15 grms. of the dried material corresponding to 100 grms. of the fresh stomach. Safe clinical dose is 10 grms. for each million red cell deficit in the count. When the blood returns to normal it should be continued in 10 grm. doses four to five times a week. The best form of administration is the dry extract in some fruit juice.

Class B : **Drugs used in Microcytic Hypochromic Anæmia**

FERRUM

Iron. Fe

Syn. I.V.—*Loha*, Beng., Hind.

Source.—Iron in the form of fine bright wire having a diameter of about 0.1 millimetre.

Official Preparations

1. **Syrupus Ferri Iodidi.**—Contains 7½ grs. of ferrous iodide, or 1⅛ gr. of iron in 120 ms. **B.P. Dose.—30 to 120 ms. or 2 to 8 mils.**

2. **Syrupus Ferri Phosphatis Compositus.** *Syn.—Parrish's Food, Parrish's Syrup*; *Chemical Food.*—1⅙ gr. ferrous phosphate, or ⅛ gr iron, 1¾ gr. tricalcium phosphate in 120 ms. **B.P. Dose.—30 to 120 ms. or 2 to 8 mils.**

3. **Syrupus Ferri Phosphatis cum Quinina et Strychnina.** *Syn.—Easton's Syrup.*—Contains 1 gr. ferrous phosphate or ½ gr. iron, ⅘ gr. quinine sulphate, $\frac{1}{60}$ gr. strychnine hydroch. in 60 ms. **B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**

FERRUM REDACTUM

Reduced Iron

Source.—Obtained by the action of hydrogen on ferric oxide. Contains not less than 80 p.c. of metallic iron, or about 8 grs. of metallic iron in 10 grs.

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Characters.—A fine, greyish-black powder, free from metallic lustre, and from gritty particles. *Insoluble* in water, and in alcohol (90 p.c.); freely soluble in dilute hydrochloric acid.

B.P. Dose.—1 to 10 grs. or 0.06 to 0.6 grm.

Iron salts group themselves into three classes:—(1) Ferrous or Protosalts based upon Ferrous Oxide FeO. (2) Ferric or Persalts (sesquisalts) upon Ferric Oxide Fe_2O_3, and (3) Scale Preparations. Ferrous salts soon become ferric from the absorption of atmospheric oxygen, especially in the presence of oxidising agents, as chlorine, nitric acid, etc.

1. Ferrous Salts

FERRI CARBONAS SACCHARATUS

Saccharated Iron Carbonate

Source.—Dissolve 150 G. liquid glucose in 3000 mils of water and add ferrous sulphate 1000 G., add this to a solution of sodium carbonate 1078 in 1500 mils of water. Allow precipitate to form, wash with distilled water. Mix liquid glucose 157 G., dry at 100°. Powder the product. Contains not less than 50 p.c. iron carbonate, or 7½ grs. of iron in 30 grs.

Characters.—An olive-brown, slightly hygroscopic powder; taste, feebly chalybeate. Partially *soluble* in water, soluble with effervescence in dilute hydrochloric acid.

Incompatibles.—Vegetable astringents, acids and acid salts.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grm.

Non-official Preparation

1. **Massa Ferri Carbonatis, U.S.P.** *Syn.—Vallet's Mass.*—Ferrous sulphate 100; monohydrated sodium carbonate 46; honey 38; sucrose 25; syrup and water each *q.s.* to 100. Contains not less than 35 p.c. ferrous carbonate. *Dose, U.S.P.*—0.25 grm. or 4 grs.

FERRI SULPHAS

Ferrous Sulphate. $FeSO_4,7H_2O$

Syn. I.V.—*Hirakas*, Beng. *Hira Kasus*, Hind.

Source.—Prepared by the action of diluted sulphuric acid upon iron. Contains not less than 99 p.c. of pure sulphate.

Characters.—Transparent, green crystals; or a pale, bluish-green powder; metallic, astringent taste. *Solubility.*—1 in 1½ of water.

B.P. Dose.—1 to 5 grs. or 0.06 to 0.3 grm.

Official Preparations

1. **Ferri Sulphas Exsiccatus.**—Ferrous sulphate deprived of part of its water of crystallisation by drying at a temperature of 40°. Contains not less than 80 p.c. ferrous sulphate. 3 grs. contain about 1 gr. of iron. A greyish-white powder, slowly but completely soluble in boiled and cooled water. **B.P. Dose.—½ to 3 grs. or 0.03 to 0.2 grm.**

2. **Pilula Ferri Carbonatis.** *Syn.—Blaud's Pill; Pilula Ferri.*—20 p.c. ferrous carbonate, or 3 grs. of iron in 30 grs. **B.P. Dose.—5 to 30 grs. or 0.3 to 2 grm.**

3. **Pilula Aloes et Ferri.**—Contains $\frac{4}{5}$ gr. of exsiccated ferrous sulph. or about $\frac{1}{4}$ gr. of iron, and $1\frac{3}{5}$ gr. aloes in 8 grs. **B.P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.**

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Non-official Preparations

1. **Ferri Hydroxidum c. Magnesii Oxido, U.S.P.** *Syn.—Arsenic Antidote.*—Solution of ferric sulphate 40 c.c.; mag. oxide 10 grms.; water *q.s.* to 1000 c.c. *Dose.—U.S.P.*—120 c.c. or 4 oz.

2. **Mistura Ferri Composita.** *Syn.—Griffith's Mixture.*—Ferrous sulph. 6 G., pot. carb. 8 G., myrrh, gum acacia, glucose, each 15 G., spt. nutmeg 10 mils, rose water *q.s.* 1000. *Dose.*—½ to 1 oz. or 15 to 30 mils.

2. Ferric Salts

LIQUOR FERRI PERCHLORIDI

Solution of Ferric Chloride

Source.—Obtained by the oxidation of ferrous chloride, prepared by the interaction of diluted hydrochloric acid and iron. Contains 15 p.c. w/v of $FeCl_3$, or about 2½ grs. of ferric chloride, or ⅕ gr. of iron in 15 ms.

B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

Non-official Preparation

1. **Liquor Ferri et Ammonii Acetatis, U.S.P.** *Syn.—Basham's Mixture.*—Tr. ferri perchlor. 4; acid acetic. dil. 6; liquor ammon. acetatis 50; aromatic elixir 12; glycerin 12; water *q.s.* to 100. *Dose, U.S.P.*—15 c.c. or 4 drs.

3. Scale Preparations

FERRI ET AMMONII CITRAS

Iron and Ammonium Citrate

Source.—Prepared by saturating a warm aqueous solution of citric acid with freshly precipitated ferric hydroxide, adding a slight excess of solution of ammonia, evaporating, and drying on glass plates at 40°. Contains 20.5 to 22.5 p.c. iron, or about 3 grs of iron in 15 grs.

Characters.—Thin, dark-red, transparent scales; taste, astringent, deliquescent in moist air. *Soluble* in 0.5 part of water; almost insoluble in alcohol (90 p.c.).

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Official Preparation

1. **Injectio Ferri.**—Contains $\frac{1}{10}$ gr. iron, or ½ gr. iron and ammonium citrate in 30 ms. **B.P. Dose.—15 to 30 ms. or 1 to 2 mils.**

FERRI ET QUININAE CITRAS

Iron and Quinine Citrate

Source.—Prepared by dissolving freshly precipitated ferric hydroxide and quinine in a warm aqueous solution of citric acid, adding a solution of ammonia, evaporating and drying on glass slides at 40°. Contains 14.5 to 15.5 p.c. anhydrous quinine, and 12 to 14 p.c. iron, or 2 grs. of iron and 2¼ grs. of quinine in 15 grs. Thin, greenish-yellow scales of a bitter taste. *Soluble* in 0·5 parts of water.

Incompatibles.—Alkalies and their carbonates, tannin, vegetable astringents, potassium citrate.

B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Additional Non-official Preparations and Derivatives of Iron

1. **Ferri Iodidum.**—Steel-grey or reddish-brown crystalline, hygroscopi masses. Soluble in water. *Dose.*—1 to 5 grs. or 0·06 to 0·3 grm.

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2. **Ferri et Potassii Tartras.** *Syn.—Ferrum Tartaratum.*—In transparent, garnet-coloured scales. Soluble in water. *Dose.*—5 to 10 grs. or 0·3 to 0·6 grm.

3. **Ferri Lactas.**—In greenish-white crystals, soluble 1 in 40 of water. Readily assimilated. One of the least astringent forms of iron. *Dose.*—2 to 10 grs. or 0.12 to 0.6 grm.

4. **Liquor Ferri Hypophosphitis, B.P.C.**—Solution of ferric sulph. 14·20; solution of ammonia 23; citric acid 7·60; sodium hypophos. 9·60; sod. citrate 6·60; water q.s., stronger chloroform water to 100. *Dose.*—10 to 30 ms. or 0·6 to 2 mils.

One part of this to 5 of Syrup makes **Syrupus Ferri Hypophosphitis, B.P.C.**—*Dose*—½ to 2 drs.

5. **Syrupus Hypophosphitum Compositus, B.P.C.**—1/100 gr. of strychnine and 1/8 gr. of quinine in 1 dr. Strychnine 0.01, Hypophosphorous Acid 1.25. Dissolve, and add it to the following solution:—Calcium Hypophosphite 0.91; Manganese Hypophosphite 0.46, Potassium Hypophosphite 0.46, Quinine 0.22, Chloroform Water 10. Add solution of Iron Hypophosphite 5, Sugar 70, dissolve without heat, and add Chloroform Water *q.s.* to 100. *Dose.*—1 to 2 drs. or 4 to 8 mils.

6. **Injectio Ferri et Arseni, B.P.C.** *Syn.—Injection of Iron and Arsenic.*—Strong solution of ferric chloride, 1.75 mil.; citric acid, 2.0 gm.; arsenic trioxide, 0.13 gm.; dilute solution of ammonia, *q.s.*; sterile water to 100 mil. Contains about 1/50 gr. of arsenic trioxide in 15 ms. *Dose.*—0.5 to 1 mil. or 8 to 15 ms. intramuscularly.

7. **Ferri, Quininæ et Strychninæ Citras.**—In thin, transparent, deliquescent, greenish or golden-yellow scales with an intensely bitter and ferruginous taste. Soluble 1 in 2 of water. *Dose.*—0.12 to 0.3 gm. or 2 to 5 grs.

Pharmacology of Iron and its Salts

Externally.—Iron salts have no action on the unbroken skin, and are not absorbed by it. Ferrous and organic salts are feebly astringent. A solution of ferric salts when applied to a denuded surface, mucous membrane, sores or ulcers, coagulates the albuminous secretion, as well as the albumin of the tissues. It also coagulates blood and plasma. The circulation of the part is greatly reduced by the compression of the coagulated albumin from outside and not by the contraction of the muscular fibres of the walls of the blood-vessels. If there is any hæmorrhage, it is readily arrested by (1) the compression of the blood-vessels from without, and (2) the plugging of the bleeding vessels by the clotting of the blood within them. Therefore it is a powerful **styptic**. It acts as an astringent or irritant according to the concentration used; the irritant effect being due to the acid ion and not to the metal. Iron however has no specific poisonous action on living matter like mercury or antimony. The perchloride, the pernitrate and the persulphate of iron are all strong local astringents. The oxides of iron convert oxygen into ozone and are therefore disinfectant.

Internally. **Mouth.**—Iron blackens the teeth and the tongue, from the deposition of iron tannate or sulphide. This is supposed to be due to tannic acid of the food precipitating black tannate of iron, or to the sulphide of iron formed by the action of hydrogen sulphide present in carious tooth. It has a styptic taste, and the ferric salts have a similar action here as on the raw skin.

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Stomach.—All iron preparations, in whatever form they are taken by the mouth, are mostly converted into chlorides in the stomach, and not into an albuminate. Even an albuminate is decomposed into a chloride. If given in large doses, or if continued for a long time, all iron salts set up irritation, pain, nausea and vomiting. Prolonged use of inorganic salts is often followed by indigestion and constipation, due no doubt to the astringent action on the alimentary canal. In the presence of gastric secretion and in the presence of easily oxidisable substances, ferric ions are reduced to ferrous. In fact all iron salts are transformed into simple ferrous compounds before they are absorbed by the duodenum and upper part of the intestine. The scale preparations however do not ionise in the stomach and therefore do not impair digestion.

Intestine.—In the lower part of the intestine the ferrous compounds coming in contact with alkaline secretions are converted into insoluble phosphates, carbonates or other complex salts which are not so easily absorbed, the unabsorbed portion being converted lower down into sulphides and tannates by the sulphuretted hydrogen and tannic acid, the latter being derived from the vegetable food, and are passed out with the fæces which are coloured black. The astringent effect is continued in the intestine, and if the dose is large, or continued over prolonged period, iron salts cause constipation.

Absorption.—In order to understand the absorption of iron it is necessary to distinguish between inorganic and organic compounds. In the inorganic salts the iron exists in the ionic form, while in the organic compounds the metal exists in the non-ionisable state. In the various double salts containing citric and tartaric acids, the iron though exists in the non-dissociable form is easily dissociated. The food iron is exclusively organic iron and exists in combination with nucleo-proteins. Plants contain iron in the organic form and take it up from the soil, where it is necessary for the formation of chlorophyll, although it is not actually contained in it as it exists in the hæmoglobin. All vegetable foods therefore contain iron.

Iron is absorbed mainly from the duodenum and to a less extent from the jejunum. Its absorption is difficult and it is generally held that the food iron is absorbed by the gastro-intestinal canal, for the growing child derives all the iron necessary for its growth and development from its food. But there was a good deal of controversy regarding the absorption of inorganic iron. All recent experiments however go to prove that inorganic iron can readily be absorbed, and the opinion is gaining ground that even the food iron requires to be broken down into more diffusible ionised form before it can be absorbed by the alimentary canal. All iron com-

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pounds are probably absorbed as ferrous ions by the intestinal epithelium and transferred to the white corpuscles of the blood, which convey them to the liver, where they are deposited and gradually elaborated into more or less complex indissociable compounds, one of which is *Ferratin*. These iron granules generally pass into the blood-stream and are utilised by the red bone marrow for the formation of hæmoglobin. The liver must be regarded not only as the storehouse for iron, but as a place where iron is worked up into complex ferruginous organic compounds. The reticulo-endothelial cells have some share in iron metabolism and utilise the iron from degenerated red cells and hæmoglobin for the formation of fresh red cells (*see* page 424). As has been pointed out iron salts coming in contact with the alkaline secretion in the lower part of the intestine are converted into insoluble phosphates, carbonates or other complex compounds which are not easily absorbed. What actually helps the absorption of iron is not clearly understood, and it has been suggested that the vital activity of the intestinal epithelial cells may to some extent have a share in the absorption. It is possible that there is some mechanism governing the absorption according to the requirements of the body, for it has been pointed out by Cloetta that when iron is deficient in food the body has the power of conserving it and utilising every trace of iron in the food, on the other hand when there is excess of iron the intestine ceases to absorb more than is required for the body.

In fact iron is stored up in the liver, spleen and bone-marrow even when injected intravenously and is subsequently excreted by the cæcum and colon. Given orally, iron may be excreted directly with the stool, or may pass through the portal circulation, absorbed into the system and retained in the liver to be subsequently excreted in the large bowel and passed out with the fæces in an organic form. The process of absorption and excretion is slow, and therefore it has been possible to trace its presence in the liver and estimate the quantity. This is done by feeding some young animals of the same litter with rice and milk only, and another lot with iron in addition to milk and rice as controls. The animals not receiving iron thrive badly and become emaciated, while those receiving extra iron show more iron in the liver. Again if an animal is given a meal containing iron and after some time it is killed and parts of the alimentary canal are hardened, the duodenum and the upper part of jejunum and rectum will show under the microscope distinct evidence of iron (either prussian blue or black granules according to stain used) in process of absorption and excretion. These granules can be traced to the mesenteric glands, the spleen, and to a less extent the liver and the cortex of the kidney. If, however, the

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animal is allowed to live longer, more granules will be found in the liver and less in the duodenum, spleen and lymphatic glands, showing that the iron has left the spleen and migrated to the liver again to be excreted *via* the large intestine and the cæcum. Lastly, it has been found that if an animal is treated with iron in whom colotomy has been performed and the lower part of the intestine is daily washed out and the washings examined, a small amount of iron will be found in the lower bowel, where it can only arrive by a process of absorption and elimination.

Older views regarding the absorption of iron are of historical interest. Buchheim held that inorganic iron was not absorbed but improved anæmia by stimulating appetite and digestion and the extra food taken supplied the necessary iron to reconstitute the blood. Bunge held a similar view. He argued that in anæmia digestion was greatly disturbed and alkaline sulphides were formed which combined with the food iron to form Fe_2S, which was an inorganic salt and therefore incapable of absorption. When iron was given in these conditions it combined with the alkaline sulphides leaving the organic iron to be absorbed. But mere stimulation of appetite and digestion by other tonics does not improve anæmia and that sulphides of iron which do not combine with alkaline sulphides cure anæmia. These views therefore are not accepted and the modern view of the absorption of iron has been given above.

Blood.—Iron is an essential constituent of every cell in the body and the normal process of cell oxidation depends upon its presence. About two-thirds of the iron in the body exists in the form of hæmoglobin. Its production therefore is intimately associated with iron metabolism. In health, iron has very little effect upon either the quantity or the quality of the blood-corpuscles, but increases the reserve iron, so that its transformation into hæmoglobin occurs only as required by the body. Thus in cases of anæmia both the number of corpuscles and their hæmoglobin value are markedly increased. Since patients suffering from chlorosis do not improve with foods containing iron, in fact chlorosis appears in persons amply supplied with food iron, but improves under inorganic iron, it has been suggested that iron acts as a chemical stimulus to the blood-forming organs, and not being an entirely foreign constituent is less injurious to the body than other stimulants. This view however has been challenged, and it has been argued that in animals rendered anæmic recovery is not accelerated by food iron as would happen if the blood-forming organs are actually stimulated by iron (Zahn). It has therefore been suggested that improvement is due to the abundance of the material supplied to the blood-forming organs. The fact remains that iron is a valuable hæmatinic. Recently the idea has been put forward that the formation of hæmoglobin depends upon the presence of minute quantities of copper in addition to iron which acts as a catalytic agent in the treatment of anæmia. An adult man contains about 3.0 to

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3.5 gms. of iron, of which about 2.4 to 2.7 gms. are in the form of hæmoglobin. About 20 mgm. is excreted daily, and this loss is replaced by the iron of the food, and a minimum of 6 to 12 mg. is required to maintain this equilibrium.

Metabolism.—With the improvement of the red blood-corpuscles there is necessarily an increased absorption of oxygen, and an increased oxidation of tissues. Hence, the functional activity of all the organs of the body is stimulated, leading to the general improvement of the tone of the body. Iron is therefore a most valuable **general tonic.** As the whole system shares in this benefit, the menstrual flow, if it had been stopped, is re-established and many disordered functions are rectified. Although these results are mainly indirect, depending upon the improvement of hæmoglobin, it should be remembered that iron is a constituent of all cells and some effects must be direct.

Excretion.—Iron salts are feebly excreted by the renal cells, and their estimation is difficult, while some found as much as 8 mgrm. daily, others estimated it less. It is excreted in largest quantity through the bowels, mainly the large intestine. On an average one milligramme is eliminated daily, and this seems to remain almost constant in all circumstances. The ferric salts slightly diminish the secretion of urine, while the other preparations have no effect, except the tartrate and the acetate, which slightly increase it. They may sometimes irritate the bladder, and may cause nocturnal incontinence of urine in children.

Therapeutics of Iron and its Salts

Externally.—Organic iron salts and ferrous salts, except the sulphate, are not locally used. Though iron salts are powerful astringents and styptics they are not much used nowadays as they cause a dirty coagulum and irritation of the tissues. The solution of perchloride mixed with equal quantity of glycerin is used as a paint for its astringent action in different conditions of the throat and tonsils, viz. enlarged tonsils, diphtheria and sore-throat. The same may be used as a gargle well diluted. A solution of ferrous sulphate (10 grs. to 1 oz. of water) is an extremely useful local application in erysipelas, but it deserves to be noted that its stain on the linen is not removed by washing. Sometimes the solution of perchloride may be painted for the same purpose. Ferrous sulphate or copperas has been used as a disinfectant for cesspits, water closets, etc. It acts by precipitating the proteins which mechanically carry down the bacteria.

Internally. **Gastro-intestinal tract.**—Because of the astringent effect on the intestine, iron salts, specially the ferric compounds, are used in diarrhœa. Chronic diarrhœa,

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rebellious to all manner of treatment, is sometimes wonderfully checked by the solution of pernitrate (5-15 ms.). It is specially useful in those cases where the patient is anæmic. Here it acts not only as an astringent but by improving the condition of the blood gives tone to the intestine. Chronic constipation may often be successfully removed by ferrous sulphate and extract of nux vomica or extract of belladonna. Humid peroxide of iron is an antidote to arsenical poisoning. It can be prepared fresh by mixing a solution of perchloride of iron 3 ozs., with bicarbonate of soda 1 oz. in solution; half an ounce of this is given every 5 or 10 minutes. Ferri Hydroxidum cum Magnesii Oxido may be given in its stead in half ounce doses diluted. An enema of the solution of perchloride of iron (1 dr. in 1 pint of water) kills thread worm.

Blood.—Iron is a valuable remedy in anæmia. The forms of anæmia which respond to iron treatment are those characterised by small size and pallor of the red cells, pallor or hypochromia due to deficient corpuscular content of iron and hæmoglobin. Iron salts are therefore extensively used in chlorosis, scrofula, chronic nephritis, convalescence from acute and chronic illness, etc. Ferrous salts are the most potent preparations and most of the idiopathic microcytic anæmias are cured by these salts. Some cases are however refractory and do not respond to iron. This refractoriness is often due to deficient absorption from the intestine.

Anæmia and Chlorosis.—Ordinary forms of anæmia traceable to some definite cause such as scurvy, malaria, protracted hæmorrhage, lead poisoning and ankylostomiasis, etc., are materially benefited by a course of iron, as well as by the removal of the cause.

Iron is the most valuable remedy in chlorosis. Although the actual amount of food iron is not deficient in this disease, chlorotic patients are not able to assimilate enough iron from the food; moreover owing to poor appetite and digestion, the quantity becomes still less and the body soon becomes depleted of iron causing anæmia with deficiency of hæmoglobin. There is therefore deficient supply of oxygen for the body requirements as evidenced by breathlessness, cardiac weakness and œdema. Iron by improving the condition of hæmoglobin brings on an improvement in the patient's condition. Insoluble preparations being less irritating to the stomach are tolerated better, and therefore Blaud's pill, reduced iron and saccharated iron are largely used. The scale preparations may be used in the form of mixture with equally good results. Constipation often gives trouble in this disease and is increased by the use of iron. Aloe and belladonna with pill, and magnesium sulphate with mixture answer the purpose well.

In anæmia due to blood loss, recovery generally follows

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without any use of iron, in fact loss of blood itself acts as a stimulus to the blood forming organs.

If the anæmia is due to malaria, ferri et quininæ citras, or Easton's syrup may be given with advantage. The same preparations may also be employed as a tonic during convalescence after an acute febrile attack or any other protracted illness. The following is a very useful combination, viz.—Acidum hydrochloricum dil., ms. 10; ferri et quininæ citras, gr. 5; tr. nucis vomicæ, ms. 10; spt. chloroformi, ms. 15; aqua ad oz. 1; one t.d.p.c.

Splenic anæmia.—Davidson (*Lancet*, Sept. 1934) has pointed out that although it is said that iron is of little value in this form of anæmia, it has given excellent results in this condition. He is of opinion that the three common causes of hypochromic anæmia are frequently present in this condition, *viz.* (*a*) defective intake of iron through poor diet; (*b*) deficient absorption of iron from the presence of achlorhydria; and (*c*) increased demand of iron from blood loss.

Pernicious anæmia.—Since this form of anæmia arises from the deficiency of the specific anti-anæmia factor contained in the liver, iron is of little value in this condition. Beebe and Lewis (*American Journal of Medical Science*, 1931) consider iron as an important adjuvant to liver therapy, specially in cases where there is deficiency of the anti-anæmic factor derived from the protein with deficiency of iron assimilation. Pernicious anæmia when treated with whole liver does not as a rule require iron as this organ is particularly rich in that metal. Since the introduction of the parenteral method of treatment of this disease the position has changed, as the anti-anæmic fraction does not contain any iron which is given as injection and in consequence the body's reserve store of iron is rapidly utilised inorder to supply the large requirement of the hæmoglobin synthesis which occurs during recovery. It is therefore necessary that iron should be given during the relapse stage of pernicious anæmia. And it has been found that there is a marked acceleration in the speed of recovery, both in the hæmoglobin level and in the patient's physical condition by giving 60 to 90 gr. of iron and ammonium citrate daily.

Many conditions depending on anæmia, and which are sometimes more troublesome, are benefited by a course of iron. Thus **amenorrhœa** when due to anæmia often yields to iron specially when given in combination with aloes, as Blaud's pill and pil. aloe et ferri. Similarly gastric catarrh and œdema so common in profound anæmia, also disappear with the exhibition of iron. These effects are due to improvement of hæmoglobin which follows the use of iron and not to any special action either on the stomach or the circulation. Iron being an integral part of all cells of the body, it is possible that it helps to perform their functions better when

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there is an abundant supply of this element, therefore iron is a valuable tonic. Its value is doubtful in the anæmia of *leucocythæmia, Hodgkin's disease* and *exophthalmic goitre.*

Bright's disease.—Acetate of iron is a valuable remedy in this disease. It not only improves the blood, but lessens or removes the albumin. Basham's mixture is a very useful preparation in chronic parenchymatous nephritis. With many the steel drops is a favourite remedy.

Scrofula and other tubercular affections are benefited by a course of iodide of iron.

Iron is useful in certain **septic conditions** due to streptococcal infection. The solution of perchloride is used in erysipelas, puerperal sepsis, acute tonsillitis and in other bad forms of sore-throat such as hospital sore-throat, with very good results. In these cases it is usually combined with quinine. It is also used in diphtheria.

Nervous system.—Iron cannot directly influence the nervous system, but indirectly it does by improving the nutrition and the general functions of the bodily organs. Easton's syrup, syrupus hypophosph. comp., syrupus ferri hypophsph., may be selected with advantage.

Caution.—The following points should always be remembered during the administration of iron :—

1. Iron sometimes irritates the stomach even of healthy persons.
2. Begin with one of the milder preparations and give it after meals.
3. Use it very cautiously in plethoric subjects, or in those who are predisposed to apoplexy.
4. Change your preparation from time to time during a long course of iron treatment, or stop it at intervals.
5. If iron causes constipation, combine it with purgatives.
6. If iron causes headache or indigestion, stop it at once.

Prescribing hints.—The choice of a preparation sometimes becomes difficult to a young practitioner. We have metallic iron, ferrous salts, ferric salts and the scale preparations. The student should distinguish an astringent from a non-astringent preparation and should bear in mind that there are a few, such as the iodide, arsenate, the phosphate and the citrate with quinine, whose value depends mainly or to some extent, upon the other ingredients they contain. The organic salts are non-astringent, but they have not proved so effective as the inorganic ones, as the larger molecules of these have to be broken down by the digestive juices before they can be absorbed. Of the inorganic salts the ferric salts are more astringent than the ferrous salts. Although both the organic and inorganic compounds are absorbed and produce their therapeutic effects, the ionised iron is more active therapeutically. All iron preparations should be

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given after meals, except reduced iron, which should be given before meals to enable the gastric juice to act upon it. Reduced iron does not impair digestion, but to be effective should be given in massive doses. The scale preparations are very effective preparations since they do not oxidise in solution nor irritate the stomach. They can be given in large doses, *i.e.* 15 to 20 grs. per dose, three times a day. The insoluble ferrous compounds like the Blaud's pill or ferri carbonas saccharatus are largely used, the latter preparation being very useful for children. Blaud's pill however becomes converted into ferric salt and too hard when kept long and passes through the intestine unchanged. The perchloride is considered by some as the best preparation for treatment of anæmia. But clinical experience has shown that ferrous salts act better, possibly because they are less astringent and irritant, and are less liable to impair digestion or cause constipation. In fact the opinion is gaining ground that even ferric salts require to be reduced to ferrous compound before they can be absorbed.

Since large doses of iron are required for the cure of anæmia, it is evident that the absorption of iron, when given by the mouth, must be very poor. Iron is therefore used parenterally either as injectio ferri or in combination with arsenic, as injectio ferri et arseni. Heath, Strauss and Castle* found that 32 mgrm. of metallic iron when injected was approximately equal, from the point of view of blood-building, to 1000 mgrm. of iron by mouth (90 gr. of iron and ammonium citrate). But inasmuch as the optimal parenteral dose is very near the toxic dose, the above authors recommend that in the routine treatment iron should be given by the mouth. Except in the treatment of nutritional anæmia of milk-fed infants, copper is not regarded as an adjunct in the treatment of all forms of hypochromic anæmia. Being toxic when given intravenously, iron should never be used by this route.

The perchloride is largely employed in various ways, as a gargle, pigment, spray, dressing (*e.g.*, cotton or lint soaked in solution 15 p.c.), rectal or urethral injection, or mixture. If given in a mixture, glycerin or lemon juice covers the ferruginous taste. The infusion of quassia, calumba or chiretta may be used as a vehicle as they do not contain tannin. The constipating property of iron salts is best removed by magnesium sulphate, if given in a mixture; or by aloes or rhubarb if in pill. The inky colour which results if they are combined with cinchona or digitalis, is cleared by the addition of a few drops of diluted phosphoric acid. The action of iron is not affected by this chemical change. By addition of alkali the acid reaction of the iron salts and their

* Journal of Clinical Investigation, 1932, ii

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astringency are lessened, and therefere Blaud's pill and Griffith's mixture are so well-borne. Syrupus Ferri Phosphatis and Syr. Ferri Iodidi should be given alone diluted. Syrupus Ferri Iodidi when prescribed with acids liberates iodine and with alkalies will throw down insoluble iron compounds. Ferrous sulphate is given in pill and if it is intended for action on the intestine it should be coated with keratin. To prevent the blackening of the teeth, the iron mixture should be swallowed through a glass tube or a quill. Inj. ferri, arsenite of iron, or ferri cacodylas are largely used hypodermically for the treatment of anæmia. Parrish's chemical food is an excellent preparation for children and delicate women. Citrate of iron and quinine should not be mixed with alkalies or alkaline carbonates as the quinine is precipitated.

GROUP XXIV

DRUGS ACTING ON THE SKIN

The skin is one of the most important organs of the body performing diverse functions. It protects the underlying structures, regulates body temperature by variations in the blood supply and sweat formation, and plays an important part in the general metabolism by absorbing the ultra-violet rays and utilising them in the formation of vitamin D so important for growth and nutrition. Being a highly differentiated tissue and being freely supplied with sensory nerves, it reflexly affects respiration and circulation, and any injury to the skin is followed by local and general effects depending upon the nature and intensity of the damage (*see* counter-irritants, page 610). Thus symptoms of poisoning and shock following extensive injury to the skin, as happens after burns, are attributed to the absorption of the break-down products of histamine-like substances. Skin rash is a common accompaniment of many poisons and infections, and it is possible that it plays an important part in the defensive reactions that protect the body from microbic invasion.

Sweat.—Secretion of sweat is an important function of the skin and is performed by the sweat glands. Although an excretion, inasmuch as it helps elimination of water, salts and nitrogenous end products, it regulates the body temperature by the evaporation of the water. The total amount of water lost in 24 hours is about 500 to 700 c.c. and may be greater under special circumstances. The reaction of human sweat is acid, due to the presence of fatty acids derived from the sebaceous glands. The secretion of sweat differs from the urine in that it is influenced by nerves and is independent of blood-pressure or general circulation, in fact there is abundant sweat when the skin circulation is

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almost nil, as for instance, the cold sweat and death sweat; although increase of blood volume, as happens after drinking large quantities of water, is followed by diaphoresis.

The sweat glands are supplied by the sympathetic and are also under the control of the central nervous system. Pharmacologically the peripheral mechanism of the sweat glands acts as if they are innervated by the parasympathetic. Adrenaline, which stimulates sympathetic, produces no effect on sweat secretion. Mayer and Gottlieb hold that the sweat glands receive in general augmentor nerves from both the autonomic systems, and that in man and certain animals only the parasympathetic endings are accessible to the action of drugs (*see* page 217).

Drugs that increase the secretion of sweat are called **diaphoretics** or **sudorifics.** They act as follows ;—

1. *By directly stimulating the centre.*—Drugs which stimulate the spinal centres also stimulate the spinal sweat centres. The following drugs stimulate the centres and cause diaphoresis ; they are ammonium acetate, ammonium citrate, and camphor. The centre is also stimulated by venous blood.

2. *By stimulating the nerve-endings.*—Pilocarpine is most powerful in this respect. Nicotine, physostigmine and muscarine act similarly.

3. *By dilating the cutaneous vessels.*—As by local heat, hot baths, turkish baths, hot drinks, or by drugs which specifically dilate vessels of the skin, as alcohol, opium, (Dover's powder), chloral, salicylates, acetanilide, etc.

4. *Reflex stimulation of the centre.*—Stimulation of the throat and stomach, as by tickling the throat or by the use of emetics, such as antimony and ipecacuanha, will produce perspiration through reflex stimulation. Other examples of this are sweating in nausea and during psychical stimulation of the cerebrum, as from fear or anxiety.

Therapeutics.—Diaphoretics are indicated :—

(*a*) To reduce pyrexia.

(*b*) To cut short a threatening catarrh, or inflammation caused by specific poisons or metabolic products.

(*c*) To lessen the accumulation of fluid in the system, as in dropsy, and to relieve excretory organs, *e.g.* kidneys in albuminuria.

(*d*) To eliminate excrementitious products through the skin when the action of the kidneys is suspended, as in uræmia. Pilocarpine is most useful for this purpose.

(*e*) To promote cutaneous circulation in many chronic skin diseases, *e.g.* warm water or Turkish baths in psoriasis.

Drugs which diminish the sweat are known as anhidrotics. They may act as follows :—

1. *By depressing the ends of the secretory nerves* (*parasympathetic*). The effect of atropine is most powerful.

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2. *By lessening the activity of the sensory nerves*, as by cold application, cool atmosphere, etc.

Some drugs like acids, quinine, nux vomica are also used but their mode of action is not known.

Drugs that affect the hair.—The hairs are epidermal growths contained in pits or hair-follicles. Except certain parts, the whole body surface is covered with hairs. But the growth of hair on the scalp, face, axillæ and in the regions of the external genitals are controlled in a varying degree by the sex hormones. The pituitary and thyroid glands also influence the growth of hair. The influence of nerves on the growth of hair has not been satisfactorily established.

When baldness is due to defective nutrition as happens after prolonged illness, general tonics and stimulating applications like cantharidin, rosemary, capsicum, quinine and pilocarpine in the form of lotions are useful. When due to metabolic disturbance, the use of drugs to supply the deficient internal secretion like thyroid or pituitary is indicated.

Depilatories are drugs used to remove hairs. These may be (*a*) *local*, and the effects depend upon the presence of a sulphide and an alkali. The freshly prepared paste is applied in a thick layer over the part and allowed to remain for 5 to 10 minutes and then scraped off with a blunt knife, and cold cream applied to the inflamed skin. Barium sulphide (*see* page 103) is largely used for the purpose. It dissolves the hair shafts and causes them to break off leaving the skin quite clean and bald; (*b*) *internal*, *e.g.* thallium (*see* page 130).

Class A: Irritants and Counter-irritants

These are drugs or measures which relieve inflammation or congestion of some internal organs by producing local irritation. The use of irritants for various purposes is one of remote antiquity, but the method of doing this has not always been the same, yet burning with hot iron, cautery, application of blisters and the use of irritant plants to produce local irritation or inflammation are still to be found. The principle however remains, and instead of the violent methods milder remedies are now used.

All these drugs act by stimulating nerve-endings which produce (1) local vaso-dilatation and inflammation due to axon reflexes; (2) vaso-dilatation of distant organs due to axon reflexes acting through the posterior root; and (3) medullary reflexes affecting respiration and circulation (Clark).

The effects of counter-irritation are local, general and remote. The local effects may be mild being limited to production of congestion and redness of the skin, *i.e.*, rubefaction, and the drugs producing these effects are known as **rubefacients.** In this stage there is arterial and capillary

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congestion, at first active, later passive, and is usually accompanied by sensory stimulation with itching, burning and pain. These effects are axon reflexes, *i.e.*, the vaso-dilatation with all its accompaniments occur without the impulses passing through a nerve cell. The condition of the skin returns to normal without leaving any local lesion. If the irritation is too strong, or if the irritant is allowed to remain for a longer period, little vesicles appear, which eventually coalesce and form one large blister, and the drug producing this effect is known as **vesicant.** In both these conditions exudation occurs, but when the exudate is greater than can be removed by the lymphatics, it collects, forming a blister. If the application is mild or not continued long the effects following application of rubefacients or vesicants resemble those of local inflammation. If the irritation is very severe and the irritant does not penetrate the epidermis but only the cutaneous glands, pustules form, which are at first discrete but later become confluent, and the drugs which produce these effects are known as **pustulants,** *e.g.* tartar emetic and croton oil. **Caustics** or **escharotics** destroy the vitality of the part on which they are applied. They cause sloughing and inflammation of the surrounding area, *e.g.* zinc chloride, potassium or sodium hydroxide.

Apart from local effects the drugs of this group produce certain general changes, due to reflex stimulation of the vital medullary centres, *viz.*, the cardiac, vaso-motor and respiratory. The results are not uniform and depend upon the intensity of the irritation produced. A mild irritation accelerates the heart and raises the blood-pressure; while a more powerful irritation slows the heart through vagus stimulation with fall of pressure through enormous dilatation of the splanchnic vessels. Similarly respiration is stimulated by mild irritation, *e.g.* use of sinapism, or application of cold douche on the face in narcotic poisoning, faintness, or hysteria. Owing to the changes in the distribution of the blood through vaso-motor disturbance, the temperature varies. There is leucocytosis specially after the use of vesicants, while the absorption of oxygen and elimination of carbon dioxide are augmented.

The exact manner in which the counter-irritants act and exert their beneficial effects on distant organs is still a matter of dispute. Much light has however been thrown by the works of Head and Mackenzie, who have shown a relationship between the viscera and certain skin areas and body wall through the nervous system. They pointed out that the tenderness of the superficial tissues may be a manifestation of inflammation or injury of one of the internal organs. Thus tenderness of the skin and muscle of the epigastrium implies ulcer of the stomach. In many instances the pain is referred to situations remote from the organs giving rise to it. Thus

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the pain of biliary colic may be felt in the epigastrium, that of renal colic in the testicle, that of heart affections in the left arm. These tender areas or Head's areas do not correspond to posterior nerve roots but to their segmental relations. According to Head the spinal cord and brain are regular segments, and that a lesion implicating a nerve from a particular segment affects all the nerves whose centres are in that particular segment. It is possible that the good effects which follow application of counter-irritants may be the result of conferred hypersensitiveness to stimuli, to reflex changes in the circulation, or perhaps to psychical effects on the mind.

Therapeutics.—Counter-irritants are indicated as follows :—

(1) To subdue inflammation or to afford relief to the circulation of a part or organ in direct vascular connection with the skin selected for the application of rubefacients or vesicants ; *e.g.* the application of a blister in acute pneumonia, pleurisy, hepatitis, etc.

(2) To help absorption of subjacent or subcutaneous morbid growths or effusion, *e.g.* the application of flying blisters in pleuritic effusion and synovitis, and of iodine in enlarged glands.

(3) To relieve pain from neuralgia, *e.g.* sciatica and facial neuralgia.

(4) To allay central nervous irritability, as in hysteria.

(5) To reflexly stimulate the central nervous system ; as in syncope, narcotic poisoning.

(6) To relieve muscular irritability, *e.g.* sinapisms in cramps of cholera, and lumbago.

(7) To remove any morbid process from the seat of disease to the irritated surface ; as the application of a mustard plaster to the great toe or foot when gout attacks important organs. When counter-irritants act in this manner, they are called *revulsives* or *derivatives*.

CANTHARIDINUM

Cantharidin. $C_{10}H_{12}O_4$

Source.—Obtained from various species of *Cantharis* (Spanish fly), or of *Mylabris*.

Characters.—Colourless, glistening crystals ; inodorous. Very slightly soluble in water, petroleum spirit, or alcohol (90 p.c.). More soluble in chloroform, acetone and fixed oils.

Official Preparations

1. **Emplastrum Cantharidini.** *Syn.—Blistering Plaster.*—0.2 p.c. cantharidin.
2. **Liquor Epispasticus.** *Syn.—Blistering Liquid.*—0.4 p.c. cantharidin.

Pharmacology

Externally.—Locally applied to the skin, cantharidin does not show any sign of action until after 2 or 3 hours, when

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tingling and burning are felt on the part, soon followed by redness; referable to the irritation of the local nerves and the dilatation of the local blood-vessels. Vesicles appear next which run together and form one large bleb. Hence it is an **irritant, rubefacient** and **vesicant**, but its action is slower than many others of the same class. Cantharidin is freely absorbed by the skin.

Internally. **Gastro-intestinal canal.**—Unless given in very minute doses well diluted, cantharidin in the form of tincture (dose, 2 to 5 ms.) causes severe irritation of the mouth, fauces, stomach and bowels, producing burning pain in the mouth, throat and abdomen, vomiting and purging. The vomit and the motion may contain blood. Therefore it is a most powerful gastro-intestinal irritant.

Urinary organs.—Cantharidin, absorbed from the skin or stomach and bowels, is slowly excreted by the kidneys, which it stimulates and acts as a diuretic. In large doses it causes pain in the loins, and burning and scalding in the bladder and urethra leading to strangury, albuminuria and hæmaturia. These symptoms are due to active inflammation of the glomeruli, which spreads to the cells of the tubules until all the tubules are involved, and to irritation of the fundus and sphincter of the bladder.

Genital organs.—In poisonous doses it inflames the genital organs and causes violent priapism and numerous seminal emissions. It produces congestion of the uterus and may bring on menstruation or abortion.

Acute toxic action.—Besides the irritant effects on the alimentary and genito-urinary tracts already described, it affects the heart, respiration and nervous system producing quickened pulse and respiration, headache, mental confusion, loss of sensibility, convulsion, dyspnœa, and death.

Antidotes.—Emetics, pump, mucilaginous drinks, raw eggs. *Oils and fats should be avoided as they increase the solubility of the drug.* Morphine or opium suppository, and sitz bath to relieve strangury.

Chronic toxic action.—Long continued small doses cause organic changes almost similar to those that occur in phosphorus poisoning.

THERAPEUTICS

Externally.—Therapeutic indications of counter-irritants having been fully described, only some of the specific uses of cantharidin are given below:—

1. *To increase local circulation and thereby promote local nutrition*, cantharidin is used well diluted in the form of hair lotions or hair-oils in the falling off of hair and alopecia.

2. *To relieve pain* of neuralgias, blisters should be applied over the posterior branch of the spinal nerve-trunk close to the spine, for if they are put on the seat of pain, they intensify the suffering. In sciatica they may be used as flying blisters along the course of the nerve. If pain is caused by a localised inflammation, it is relieved by the

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direct application of a blister over the seat of inflammation, as in acute articular rheumatism.

3. *To promote absorption of morbid products*, blisters may be applied over the joints in chronic rheumatism, synovitis and arthritis; over the chest in pleuritic or pericardial effusions; over the abdomen in subacute peritonitis, ovaritis, pelvic cellulitis, etc.

4. *To reduce inflammation*, a blister should be applied a little away from the seat of inflammation, as in pericarditis and pleuritis in thin subjects. Counter-irritation behind the ear or high up on the temple reduces inflammation of the eyes, and on the perineum relieves prostatitis.

5. *To arrest spasm and reflex disturbances, e.g.* blisters over the epigastrium in obstinate vomiting.

Internally.—Cantharidin is only rarely used internally because it is such a powerful irritant.

Caution.—Cantharidin blisters should be avoided or very cautiously applied to children; weak, anæmic and old persons, pregnant women and those who are subject to renal disease, as they may cause strangury. Neither should they be applied to the back of bedridden patients or to paralysed limbs, as they may produce troublesome sores.

Prescribing hints.—To prevent absorption of the cantharidin, the plaster should only be kept on till the vesicles form (about 3 to 5 hours), when a hot poultice will help the rising of a bleb. It is then generally punctured to let out the serum and dressed with cold cream or soft paraffin. Sometimes we apply flying blister, *i.e.*, a series of small blisters, each not larger then a shilling or eight anna bit, kept on for about two hours in one spot, then removed and applied a few inches away for two or three hours, and so on until the affected area is covered. Before applying a blister, the skin should be thoroughly washed with soap and water and rubbed with a towel until the part becomes reddened. The plaster sometimes requires warming before application.

Class B: Emollients and Demulcents

Emollients are drugs which soften or relax the parts to which they are applied. They are bland, oily and fatty substances and prevent cracking of the skin by supplying it with fat or moisture. *Demulcents* protect mucous membranes from irritation.

Emollients and demulcents are:—

Olive Oil, Sesame Oil, Cottonseed Oil, Almond Oil, Linseed Oil, Arachis Oil, Glycerin, Honey, Liquorice, Acacia, Tragacanth, Starch, Soap, Paraffin, Oleic Acid, Lard, Wool Fat, Suet, Beeswax

OLEUM OLIVAE

Olive Oil

Source.—The oil expressed from the ripe fruit of *Olea europæa.*

Characters.—Pale yellow, or greenish-yellow, liquid with faint odour and bland taste. Sp. gr. 0.915 to 0.918.

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Composition.—(1) *Olein*, glyceride of oleic acid, 93 p.c.; and (2) *Linolein*, glyceride of linoleic acid, 7 p.c. (3) *Palmitin*, a solid oil composed of palmitic acid and glyceryl. (4) *Arachin*.

B.P. Dose.—½ to 1 oz. or 15 to 30 mils.

Official Preparation

1. **Unguentum Aquosum.**—Aqua about 24 p.c.

Pharmacology and Therapeutics

Externally.—Olive oil being a bland unirritating fixed oil is applied as an excellent emollient in dry skin diseases, such as psoriasis and xeroderma. It forms a basis for liniments and ointments, and as a lubricating agent is employed in massage. It softens and aids the removal of the scabs of eczema, favus, etc. Mixed with 4 or 5 p.c. of phenol, it is applied in the desquamative stage of scarlatina and small-pox. Lin. calcis (lime water 1, olive oil 2) is a soothing protective to burns and scalds. The oil is absorbed by the cutaneous lymphatics, and gives nutrition to the tissues, but not to the same extent as is done by cod-liver oil.

Internally.—As a demulcent, it is useful in irritant poisoning, except by phosphorus. In small doses, it undergoes the same changes in the intestinal canal as cod-liver oil and is absorbed. It is therefore a nutrient and a food, and can be given in wasting diseases. In large doses (1 to 2 ozs.) it lubricates the gut and is a mild laxative, producing painless, soft stools, and is therefore of great value in inflamed and ulcerated piles, rectal ulcers, anal fissures, and constipation, especially if produced by opium. It acts also as a laxative when given as an **enema** (4 ozs. to ½ pint of starch mucilage), and in fæcal impaction and intestinal obstruction (5 to 20 oz.). It is also used as a vehicle for rectal administration of ether and paraldehyde (*see* page 160), and for the hypodermic administration of ether and camphor (*see* pages 152 and 518).

Because the cholesterine of the gall-stone is soluble in pure olive oil at the normal bodily temperature, it has been recommended as a solvent for gall-stones on the supposition that some of the constituents of the oil are excreted with the bile, but as there is not the slightest evidence that the oil can reach the gall-stone in the gall-bladder or cystic duct its value is doubtful. 10 to 20 oz. or even more of the oil are however given daily to those who suffer from biliary calculi. It reduces the acid secretion of the stomach, and by stimulating the contraction of the gall-bladder acts as an indirect cholagogue. Its use has therefore been advocated in gastric ulcer and in dyspepsia without ulcer, but where the symptoms are similar to those of ulcer. In various disorders of the gall-bladder, such as cholecystitis without stones, cholelithiasis and in atony of the gall bladder its use relieves the symptoms.

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It may be administered alone, in capsules or in the form of emulsion.

OLEUM SESAMI

Sesame Oil

Syn.—Teel Oil; Gingelli Oil.

Source.—The oil expressed from the seeds of the *Sesamum indicum*.

Characters.—A pale yellow, liquid; faint odour; bland taste. Sp. gr. 0.921 to 0.924.

Composition.—(1) *Sesamin*, a crystalline substance. (2) Liquid fats, 70 p.c., consisting of *glycerides of oleic and linoleic acids*. (3) Sesamol, a phenol. (4) *Solid fats*, 12 to 14 p.c., stearin, palmitin, etc.

B.P. Dose.—½ to 1 oz. or 15 to 30 mils.

Uses.—Used as a *substitute for olive oil* to make liniments, ointments and plasters.

OLEUM GOSSYPII SEMINIS

Cottonseed Oil

Source.—A fixed oil obtained from the seeds of various cultivated species of *Gossypium*.

Characters.—Pale yellow, or yellow oil. Almost odourless, with a bland taste. Slightly *soluble* in alcohol (90 p.c.), miscible with ether and chloroform and with light petroleum. If it solidifies it should be gently warmed and thoroughly mixed before use.

B.P. Dose.—½ to 1 oz. or 15 to 30 mils.

Uses.—It is used for the same purposes as olive oil. Being cheap it is preferred to other oils for external use.

OLEUM AMYGDALAE

Almond Oil

Syn.—Oleum Amygdalæ Expressum, U. S. P.

Source.—A fixed oil obtained from the seeds of *Prunus communis* var. *dulcis*, or of *P. communis* var. *amara*.

Characters.—Pale yellow, nearly inodorous, with a bland, nutty taste. Sp. gr. 0.915 to 0.920. *Solubility.*—In ether, chloroform, slightly in alcohol (90 p.c.).

B.P. Dose.—½ to 1 oz. or 15 to 30 mils.

Pharmacology and Therapeutics

Externally.—Almond oil is a demulcent and emollient, and being a bland oil makes a good basis for many hair-oils and ointments. It is a soothing application for chapped hands, excoriations and irritable skin diseases.

Internally.—Sweet almond is nutritive. Its flour being devoid of starch is given to diabetic patients as a substitute for starchy food, the only objection to its use being its high price.

The oil is a mild purgative in 2 to 4 dr. doses. An enema of 1 to 3 pints of the oil is effective in impaction of fæces and obstruction of bowels. It is pleasanter than olive oil, but expense limits it use and leads to frequent adulteration.

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LINUM

Linseed

Syn.—Flax Seed : Lini Semina. **Syn. I.V.**—*Tisi*, *Mashina*, Beng. *Alsi*, Hind.
Source.—The dried ripe seeds of *Linum usitatissimum*.

Characters.—Small, brown, glossy, nearly flat seeds ; 4 to 6 mm. long ; ovate, obliquely pointed, glabrous. Internally yellowish-white with two oily cotyledons. No odour ; taste, mucilaginous, oily. Three varieties are seen, viz. brown, white and red.

Composition.—(1) *Mucilage*, 6 p.c. in the testa. (2) *Fixed oil* (*off.*), which consists of *glyceryl* combined with linoleic acid, 30 to 40 p.c.

LINUM CONTUSUM

Crushed Linseed

Syn.—Linseed Meal ; Lini Semina Contusa.
Source.—It is linseed reduced to a coarse powder. Should be recently prepared.

Characters.—A coarse brownish-yellow powder, with visible fragments of brown testa. Bland, not pungent or rancid, odour, when mixed with warm water.

OLEUM LINI

Linseed Oil

Source and characters.—A yellowish-brown oil expressed from linseed. Taste, bland ; odour, characteristic. "Boiled" linseed oil should not be used.
B.P. Dose.—½ to 1 oz. or 15 to 30 mils.

Pharmacology and Therapeutics

Externally.—Contused linseed in the form of a warm poultice is used to disperse threatening local inflammations. It acts by dilating the local blood-vessels and by relaxing the tissues relieves the tension and pain caused by pressure over the periphery of the sensory nerves. But if the poultice is too hot it increases pain and tension. If the leucocytes have already passed through the coats of the vessels, and suppuration has commenced, a warm poultice helps it to reach the surface. Hot linseed meal poultice is an excellent, mild, continuous counter-irritant for deep-seated inflammations, such as pneumonia, bronchitis, broncho-pneumonia, pericarditis, peritonitis, pelvic cellulitis, etc. The counter-irritant effect can be greatly increased by dusting powdered mustard over the surface of the poultice, or mixing it (1 in 16) with the meal.

The oil makes a good emollient application to burns and scalds in the form of carron oil (*see* page 98). It can also be used as an *enema* (1 lb.) in impacted conditions of the rectum and lower colon.

Internally.—Linseed tea, *i.e.*, the infusion of linseed, especially when combined with lemon, is a reputed domestic demulcent drink in throat cough. The ordinary formula for linseed tea is linseed 2½ drs., liquorice root 1 dr., boiling water 10 oz., infuse for two hours. This can be taken

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sweetened with sugar. It has a slightly diuretic action and a patient with an irritable bladder or suffering from gonorrhœa often finds relief by copious linseed drinks.

OLEUM ARACHIS

Arachis Oil

Syn.—Nut Oil ; Ground-nut Oil ; Pea-nut Oil.

Syn. I. V.—*China-badamer tel, Mutkalaier tel.* Hind.

Source.—Expressed from the seeds of *Arachis hypogœa.*

Characters.—Pale-yellow or greenish-yellow, liquid ; odour, faint, and nut-like; taste, bland, nutty. Sp. gr. 0.916 to 0.921. Becomes rancid and thick slowly.

Composition.—*Olein*, also contains the glycerides of *hypogœic, arachidic* and *linoleic acids.*

B.P. Dose.—½ to 1 oz. or 15 to 30 mils.

Pharmacology and Therapeutics

Externally.—The oil makes a good substitute for olive and almond oils, and has long been used in Indian pharmacy in their stead.

Internally.—It has a gentle aperient action. The seeds are very nutritive as they contain 31.0 p.c. of nitrogenous compounds, 37.8 p.c. of starch and sugar, and 11.8 p.c. of fatty matter. They are largely eaten in India and Africa.

GLYCERINUM

Glycerin. $C_3H_8O_3$

Source.—Obtained by the hydrolysis of fats and fixed oils.

Characters.—A clear, colourless, inodorous, sweet, syrupy liquid, miscible with water and alcohol (90 p.c.); insoluble in ether, chloroform, and fixed oils. It is neutral, hygroscopic ; sp. gr. 1.260 to 1.265.

B.P. Dose.—60 to 120 ms. or 4 to 8 mils ; 30 to 120 ms. or 2 to 8 mils by rectal injection.

Enters into.—The preparation of all Glycerins.

Official Preparation

1. **Suppositorium Glycerini.**—70 p.c.

Pharmacology

Externally.—Glycerin adheres to the surface to which it is applied and absorbs moisture. It keeps the part moist and does not itself evaporate. It readily penetrates the unbroken skin, and carries with it many substances, such as alkaloids, when mixed with it. It is an antiseptic, emollient and demulcent. It renders the skin supple, especially when diluted with water, allays burning or tingling. Owing to its avidity for water, undiluted glycerin is irritant to the mucous surface and to the skin. If introduced into the cervical canal, it provokes uterine contraction.

Internally. **Alimentary canal.**—Undiluted glycerin makes the mouth clammy and sticky. It is easily absorbed and

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oxidised in the body. In large doses it acts as a **laxative.** Injected into the rectum, it moves the bowels by inducing peristalsis from its local irritant effects caused by the absorption of moisture from the mucous surfaces.

Blood.—It is freely absorbed by all surfaces. Subcutaneous injections cause destruction of red corpuscles, and the hæmoglobin is dissolved in the plasma, leading to hæmoglobinuria.

Elimination.—Glycerin is excreted from the body as propionic, formic and other acids. The urine of persons taking glycerin gives the copper and fermentation tests for sugar due to the appearance of reducing product which is not sugar.

Pharmaceutical Uses and Therapeutics

Pharmaceutically.—On account of its valuable physical properties, glycerin is peculiarly fitted for pharmaceutical and dispensing uses. It makes an excellent all-round excipient for pills. It is used in the preparation of suppositories, pessaries, pastils, jellies, glyco-gelatin preparations and ointments; and as a solvent for many alkaloids, active principles, acids, alkalies, neutral salts, glucosides, iodine, etc. It is a valuable adjunct to lotions for the skin and the hair. As a flavouring agent it is largely employed as a substitute for syrups in mixtures. As a sweetener and preserver of mixtures it is admirably suited to the Indian climate.

Externally.—As an *emollient*, glycerin diluted with water (1 in 3), or glycerinum c. aqua rosæ (glycerin 2, rose water 3), is the best application for chapped lips and hands, rough, dry, furfuraceous skin and for every kind of skin disease, such as herpes, eczema, etc., which requires an emollient. Mixed with boric acid it is serviceable in pityriasis of the body and scalp. It removes dryness of the meatus of the ear, and heals excoriation and fissures. It is the best preventive for bed-sores when gently rubbed into the parts before they become tender and red. A 5 p.c. solution of both glycerin and Friar's Balsam in rose water prevents a further breaking out of acne when once it is checked. Cotton-wool soaked in glycerin and applied to the os uteri, by causing a copious watery discharge, relieves congestion of that organ. For its hygroscopic property it forms a valuable ingredient of cataplasma kaolini.

Internally. **Alimentary canal.**—The lips, the tongue and the gums covered with sordes, as in acute febrile diseases are easily cleaned by keeping them moist with glycerin. As a laxative it is never used by the mouth, but it may be combined with castor oil to render the latter less disagreeable and more effective. Glycerin (1 to 4 drs.) may be injected into the rectum by a special syringe to open the bowels in

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constipation. The official suppository may conveniently be used for the same purpose and is particularly useful in cases where there is a prejudice against the use of enemata. The injection of glycerin is contra-indicated in piles and is useless if the fæcal accumulation is very high up.

Lungs.—A tea-spoonful of glycerin alone or diluted with water often relieves cough. A little lemon juice added to it makes it more efficacious and moderates its sweetness.

MEL DEPURATUM

Purified Honey

Source.—Commercial honey melted and strained, the specific gravity being adjusted to 1.36 by the addition of water.

Characters.—A viscid, translucent, pale-yellow or yellowish-brown, liquid, becoming crystalline and opaque. Odour honey-like. Taste, sweet.

Composition.—A mixture of several kinds of sugar, *viz.* cane-sugar, grape-sugar, lævulose ; also wax, pollen, colouring and odorous matters, etc.

Enters into.—Mel Boracis, Oxymel Scillæ.

Official Preparation

1. **Oxymel.—B.P. Dose.—30 to 120 ms. or 2 to 8 mils.**

Pharmacology and Therapeutics

Externally.—Honey is a demulcent and is used as a covering to boils and excoriations. It is also used as a cosmetic.

Internally.—It increases the secretions of the mouth and throat, and acts as a demulcent, relieving dryness of the mouth, cough, difficulty in swallowing. Hence it is used in gargles, cough mixtures and linctuses. It is a nutrient and in large doses a laxative and is therefore used to open the bowels of infants. Honey makes an excellent vehicle for castor oil and for administration to new-born babes and infants.

GLYCYRRHIZA

Liquorice

Syn.—Glycyrrhizæ Radix.

Syn. I.V.—*Jashthimadhu,* Beng. *Meetha lekri*, Hind.

Source.—The peeled root and peeled subterranean stem of *Glycyrrhiza glabra*, and other species.

Characters.—Long, cylindricial, before being peeled dark brown, and longitudinally wrinkled ; when peeled, yellow, fibrous. Fracture, fibrous. Odour, faint. Taste, characteristic, sweet, free from bitterness.

Composition.—(1) *Glycyrrhizin*, a sweet, white, crystalline powder consisting of calcium and potassium salts of glycyrrhizic acid. Also contains *asparagin*, grape sugar, resin, starch, malic acid, etc.

B.P. Dose.—15 to 60 grs. or 1 to 4 grms.

Official Preparations

1. **Extractum Glycyrrhizæ.—B.P. Dose.—10 to 30 grs. or 0·6 to 2 grm.**
2. **Extractum Glycyrrhizæ Liquidum.—B.P. Dose.—30 to 60 ms. or 2 to 4 mils.**
3. **Pulvis Glycyrrhizæ Compositus.** *Syn.—Pulvis Pectoralis.*—Liquorice and senna leaf each 16 p.c. **B. P. Dose.—60 to 120 grs. or 4 to 8 grms.**

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Non-official Preparation

1. **Mistura Glycyrrhizæ Co., U.S.P.** *Syn.—Brown Mixture.*—Fluid extract of liquorice 120 c.c.; potassium antimony tartrate 0.24 grm.; tr. camphor. co. 120 c.c.; spirit of nitrous ether 30 c.c.; glycerin 120 c.c.; water q.s. to 1000 c.c. *Dose, U.S.P.* 4 c.c. or 1 dr.

Pharmacology and Therapeutics

Internally.—Being sweet it increases the flow of saliva. It is an excellent **demulcent**, and is largely employed in relieving sore-throat, for which purpose pieces of "stick liquorice" are kept in the mouth. The dried root has no laxative effect, but pulv. glycyrrhizæ co. is a mild laxative owing to senna and sulphur. Liquorice makes an excellent excipient, and disguises the taste of many nauseous drugs such as aloe, ammonium chloride, cascara sagrada, senna, senega, turpentine, and many bitter substances.

ACACIA

Acacia

Syn.—Acaciæ Gummi.

Syn. I.V.—*Gand*, Beng, *Babul-ka-gand*, Hind.

Source.—A gummy exudation from the stem and branches of *Acacia Senegal*, and other species of *Acacia*.

Characters.—Ovoid or round tears or masses; colourless, glistening, or yellowish angular fragments; odourless; taste, bland; mucilaginous. *Solubility.*—Entirely in water, insoluble in alcohol.

Composition.—*Arabin* or arabic acid, combined with calcium, potassium, and magnesium. Also contains oxidising, peroxidising, and diastatic ferments.

Official Prrparations

1. **Injectio Sodii Chloridi et Acaciæ.**—Contains 6 p.c acacia.
2. **Mucilago Acaciæ.** *Syn.—Mucilage of Gum Acacia.*—40 p.c. **B.P. Dose.—60 to 240 ms. or 4 to 16 mils.**
3. **Pulvis Tragacanthæ Compositus.**—Acacia 20 p.c. **B.P. Dose.—10 to 60 grs. or 0.6 to 4 grm.**

Non-official Preparation

1. **Syrupus Acaciæ, B.P.C.**—Mucilage of acacia 25, Syrup to 100.

Pharmacology and Therapeutics

Gum acacia is feebly nutritive, being converted into sugar in the intestine. It is given as an emollient in sore-throat, catarrhal states of the gastric, intestinal or bronchial mucous membranes and as a demulcent in irritant poisoning. It is a reflex expectorant. In pharmacy, it is chiefly used to suspend insoluble powders, resins, oils, and as an excipient for pills, jujubes, etc. The injection has been used intravenously in shock following hæmorrhage (*see* page 83).

TRAGACANTHA

Tragacanth

Syn.—Syrian Tragacanth.

Source.—A gummy exudation obtained by incision from *Astragalus gummifer*, and other species of Astragalus.

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Characters.—Thin flattened flakes, irregularly oblong, or more or less curved marked on the surface by concentric ridges, 2.5 cm. long, and 12 mm. wide; white, or pale yellowish-white, semewhat translucent. Very tough and must be heated to 49°C. before it can be powdered. Without smell or taste. *Solubility.*—Sparingly in cold water which converts it into a gelatinous mass; coloured violet by iodine.

Composition.—The part soluble in water consists of *Polyarabinan trigalactan-geddic acid*, which on hydrolysis yields *arabinose*, *galactose*, and *geddic acid*. The insoluble portion yields *α-* and *β-tragacanthanxylan-bassoric acids*, which yield on hydrolysis *tragacanthose*, *xylose* and *bassoric acid*. A little starch.

Official Preparations

1. **Mucilago Tragacanthæ.**—Tragacanth 1·25 p.c. **B.P. Dose.—60 to 240 ms.** or 4 **to 16 mils.**
2. **Pulvis Tragacanthæ Compositus.**—Tragacanth 15 p.c. **B.P. Dose.—10 to 60 grs. or 0.6 to 4 grm.**

Non-official Preparations

1. **Linimentum Exsiccans.** *Syn.—Bassorin Paste.*—Tragacanth 5, Glycerin 2, Alcohol (90 p.c.) 10, Water to 100. Dries quickly on the skin producing a pleasant cooling sensation. May be medicated with any drug.
2. **Gelanthum** (Unna).—Soak tragacanth 2½ dr. in water 10 oz. for 4 hours in a steam bath, press through muslin, add glycerin 6 dr. Heat on a water bath for 1 hour, add thymol water q.s. to 12 oz.

Pharmacology and Therapeutics

In the form of Unna's Gelanthum, or the various "Bassorins" tragacanth is very useful in the treatment of many skin diseases. It is a demulcent, and mixed with glycerin forms a soothing application in sore-throat, but its chief use is to aid the suspension of heavy insoluble powders in mixtures. As a rule the mucilage is to be preferred to the compound powder which, on account of the starch it contains, is apt to ferment.

AMYLUM

Starch

Syn. I.V.—*Shetsar*, Beng.

Source.—Polysaccharide granules, obtained from the grains of maize, *Zea Mays*.

Characters.—In fine, white powder or in irregular, angular masses; inodorous. Readily reduced to powder.

Incompatible.—Iodine

Official Preparation

1. **Glycerinum Amyli.**—8·5 p.c.

Pharmacology and Therapeutics

Externally.—Starch is bland and non-irritating and may be used as a protective and absorbent in weeping eczema or excoriated and inflamed surfaces, as slight burns. In the form of violet powder, which is merely perfumed starch, it is used to prevent excoriation of the skin of infants. Generally it is used as a basis for dusting powders and insufflations.

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Glyc. amyli is a good application for chilblains and chapped hands.

Internally.—It is a food and an antidote for poisoning by iodine. Mucilage of starch (1 in 40) forms a basis for enemas and to suspend insoluble powders and oils. It is also used as an antidote for poisoning by iodine. It should always by freshly prepared. In the form of barley water starch is largely used as a demulcent and for diluting milk for infants.

SAPO ANIMALIS

Curd Soap

Source.—Made from sodium hydroxide and purified solid animal fats, consisting principally of stearin,

Characters.—Yellowish-white or greyish-white, substance; nearly inodorous; horny and pulverisable when dry, easily moulded when heated. Soluble in alcohol (90 p.c.), sparingly in cold, but soluble in hot water.

SAPO DURUS

Hard Soap

Syn.—Castile Soap; Olive Oil Soap.

Source.—Soap made from sodium hydroxide and olive oil.

Characters.—A greyish-white, yellowish-white, or greenish-white substance; nearly odourless. Becomes horny and pulverisable when dry. Soluble in 20 parts of cold water, in 1.5 parts of hot water, almost completely soluble in alcohol (90 p.c.).

SAPO MOLLIS

Soft Soap

Syn.—Green Soap.

Source.—Soap made with potassium hydroxide and olive oil.

Characters.—Yellowish-white to green, almost inodorous, of an unctuous consistence. *Solubility.*—Readily in alcohol (90 p.c.), and in water.

Official Preparation

1. **Linimentum Saponis.** *Syn.*—*Opodeldoc.*—Soap 8 p.c.

Non-official Preparation

1. **Liquor Saponis Æthereus, B.P.C.** *Syn.*—*Æther Soap.*—Oleic acid 35, Caustic Potash. *qs.*, Water *q.s.*, Oil of Lavender 0.2, Alcohol (90 p.c.) 15, Ether to 100. For surgical use prior to operations.

Pharmacology and Therapeutics

Externally.—Soap is a valuable cleansing agent due to partial hydrolysis and formation of free alkali when it comes in contact with a large quantity of water. This alkali saponifies and dissolves the fat of the skin and softens the epidermis. It is therefore largely used in various skin diseases to remove the epidermis and to make the deeper layers accessible to other remedial measures. Owing to its power of penetration, it is used as a vehicle for drugs

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intended to be absorbed or to act through the skin. Seborrhœa, scaly eczema, sycosis and ichthyosis do well when the parts are washed with soft soap before any remedial agents are applied. The liniment rubbed over sprained or stiff joints promote the absorption of inflammatory products, but how far this effect is due to the friction or to the drug, is difficult to say. Soaps can be medicated with various drugs. Mollin or superfatted soap is not irritant and may be used in many skin diseases, and makes a good basis for ointments.

Internally.—Hard soap is **antacid**, and not being easily soluble may be used to neutralise acid in any part of the intestinal tract, which the soluble alkalies cannot reach. It aids the emulsification of foods in the duodenum, and restores some of the normal constituents of bile. It is itself a gentle laxative, and corrects and aids the action of certain purgatives, such as jalap and aloes. Introduced into the rectum in the form of a cone as a suppository, it purges by reflexly contracting the rectum and colon, and is very useful in infantile constipation. Soap and warm water make an effective enema for constipation of adults.

Hard soap is used in pharmacy as a corrigens and as a basis for pills and plasters, and the soft soap as a basis for some liniments.

PARAFFINUM DURUM

Hard Paraffin

Syn.—Paraffin wax.

Source.—A mixture of solid hydrocarbons, obtained from petroleum, and from shale oil.

Characters.—A colourless or white, translucent mass; odourless even when freshly cut; tasteless; slightly greasy to touch. Burns with a luminous flame. *Insoluble* in water and in cold alcohol (90 p.c.); soluble in ether and chloroform.

Official Preparations

1. **Unguentum Paraffini.**—Hard paraffin, white or yellow soft paraffin, white beeswax.
2. **Unguentum Simplex.**—Hard paraffin, white or yellow soft paraffin, wool fat.

Uses

In pharmacy it is used as a basis for ointments, specially for use with drugs not intended to be absorbed. It is also used as an **excipient** for silver nitrate and permanganate of potash pills.

PARAFFINUM LIQUIDUM

Liquid Paraffin

Syn.—Liquid Petrolatum, U.S.P.; Adepsin Oil; Glymol; Oleum Deelinæ; Paroleine and Chrismaline.

Source.—It is a mixture of liquid hydrocarbons, obtained from petroleum.

Characters.—Transparent, colourless, tasteless, odourless, oily liquid. Sp. gr. 0.880 to 0.895.

B.P. Dose.—1/4 to 1 oz. or 7.5 to 30 mils.

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PARAFFINUM MOLLE ALBUM

White Soft Paraffin

Syn.—Petroleum Jelly.

Source.—A mixture of semi-solid hydrocarbons, obtained from petroleum, and bleached.

Characters.—A white, translucent, soft mass; unctuous to touch. Odourless and tasteless.

Official Preparation

1. **Unguentum Aquosum.**—Aqua 24 p.c.

PARAFFINUM MOLLE FLAVUM

Yellow Soft Paraffin

Source.—A mixture of semi-solid hydrocarbons, obtained from petroleum.

Characters.—A pale yellow to yellow, translucent, soft mass. Unctuous to the touch. Almost free from odour or taste. Insoluble in water, in alcohol (90 p.c.), soluble in ether and chloroform.

Pharmacology and Therapeutics

Externally.—Paraffins neither irritate the skin, nor become rancid, nor are they acted upon by acids, alkalies or oxidising agents. They are therefore superior to lard, and form a valuable basis for ointments meant for local action only. As they are very feebly absorbed, they cannot be used as a basis where constitutional action of drugs is intended. Liquid paraffin is a useful solvent for many drugs intended for hypodermic injection. Hard paraffin is used to give consistence to softer ointments, especially in India during the hot weather. As they are non-irritant and do not undergo a change by exposure to the air, they are very useful lubricating and protecting agents in psoriasis, xeroderma, chapped hands and nipples, eczema, sunburn, etc. Paraffin forms an excellent dressing for **burns**. A thin film of liquid or melted paraffin is painted on the clean burn and then covered by a thin layer of cotton-wool which is covered by a second layer of paraffin. The dressing is renewed daily and is easily removed. It is largely used in the form of **Ambrine** which contains 5 p.c. oil of amber.

Internally.—Cocaine, menthol, ephedrine, etc., are dissolved in liquid paraffin for application as a spray to the throat in laryngeal affections. Liquid paraffin is given with the hypophosphites in the form of an emulsion as a substitute for cod-liver oil, but beyond their forming a bland basis, very little is known of their effects in the tissues. Taken internally it is not absorbed, but softens and increases the bulk of the fæces. It is mildly **laxative** and is largely used as a lubricant in habitual constipation, colitis, ulcerations of the bowels, etc., in 4 to 8 dr. doses. A disagreeable effect of giving liquid paraffin is that it is sometimes passed out involuntarily with the expulsion of the flatus.

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ACIDUM OLEICUM

Oleic Acid

Syn.—Hydrogen Oleate.

Source.—May be obtained by hydrolysis of fats, or of fixed oils, and separation of the liquid acids by expression.

Characters.—Colourless or yellowish, oily liquid; odour and taste, characteristic. Darkens on exposure. *Insoluble* in water, soluble in alcohol (90 p.c.), ether, chloroform, benzene.

B. P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

Action and Uses

Oleic acid penetrates the skin more readily than fixed oils and fats, and is therefore used in pharmacy for compounding ointments containing metallic oxides and alkaloids. In the form of capsules (7½-15 ms.) it is given by the mouth on an empty stomach every morning in **hepatic colic** and to prevent formation of **gall-stones.**

ADEPS

Lard

Syn.—Adeps Præparatus.

Source.—The purified internal fat of the hog, *Sus scrofa*.

Characters.—A soft, white, homogeneous, unctuous substance. Entirely soluble in ether.

Composition.—(1) *Olein*, 60 p.c. (2) *Stearin*. (3) *Palmitin*.

Official Preparation

1. **Adeps Benzoinatus.**—Benzoin 3 p.c.

ADEPS LANAE

Wool Fat

Syn.—Anhydrous Lanolin.

Source.—It is the purified anhydrous fat-like substance obtained from the wool of sheep.

Characters.—A pale-yellow, tenacious, unctuous substance; with a characteristic, faint odour. *Insoluble in water*, sparingly soluble in cold alcohol (90 p.c.), freely soluble in ether and chloroform.

Official Preparation

1. **Adeps Lanæ Hydrosus.** *Syn.—Lanolin.*—As a basis for ointment.

Action and Uses

Lard and wool fat are largely employed in pharmacy for making certain ointments. They are **emollients.** Adeps lanæ is non-irritant and is readily absorbed, and is therefore used as a basis for the ointment of many active drugs.

SEVUM

Suet

Syn.—Mutton Suet, Sevum Præparatum.

Source and characters.—The purified internal fat of the abdomen of the sheep, *Ovis aries*. Firm, white, unctuous. Taste, bland, nearly inodorous.

Composition.—(1) *Olein*, 30 p.c. (2) *Palmitin*. (3) *Stearin*.

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CERA FLAVA

Yellow Beeswax

Syn. I.V.—*Mom*, Beng.

Source and characters —Obtained from the honeycomb of the bee, *Apis mellifica*. Firm, yellowish. Odour, agreeable, honey-like. Not unctuous to touch. Fracture granular, not crystalline. *Solubility.*—In chloroform, and in fixed and volatile oils.

Composition.—(1) *Myricin* (melissyl palmitate), 80 p.c. (2) *Cerotic acid*, 15 p.c.

CERA ALBA

White Beeswax

Source and characters.—In white translucent masses or cakes, made by bleaching yellow wax.

Action and Uses

They are chiefly used as a basis for plasters and ointments. If the basis of the latter becomes too soft on account of the prevailing high temperature, extra white beeswax or yellow beeswax may be added to render it more suitable for use.

GROUP XXV

CERTAIN DIAGNOSTIC AGENTS

Class A : Drugs used for X-ray diagnosis

1. For the alimentary canal : **Barium Sulphate** (*see* page 102), **Bismuth Salts** (*see* page 464)
2. For the gall-bladder : **Iodophthalein**
3. For kidney affections : **Uroselectan, Abrodil**
4. For lungs and bronchioles : **Lipiodol**

Class B : Drugs used for investigating liver or kidney functions

1. Investigation of metabolic functions of liver : **Lævulose** (*see* page 568)
2. Investigation of renal efficiency : **Urea** (*see* page 382), **Indigo carmine** (*see* page 543), **Methylene Blue** (*see* page 542), **Phenol Red**

IODOPHTHALEINUM

Iodophthalein

Syn.—Iodo-ray. Opacin.

Source.—Di-sodium salt of tetraiodophenolphthalein. Prepared by the iodination of phenolphthalein. Contains not less than 86 p.c. of phthalein. The separated phthalein contains 61 to 62 p.c. of iodine.

Characters.—A blue or blue-violet, crystalline powder. Odourless; taste, saline astringent. *Soluble* in 7 parts of water. Slightly soluble in alcohol (90 p.c.).

B.P. Dose.—0.04 to 0.06 grm. per kilogram of body weight up to 8 grms. or $\frac{1}{15}$ to $\frac{1}{12}$ gr. per pound of body weight up to 75 grs. For *intravenous injection* up to 3 grms. or up to 45 grs.

Uses

Given intravenously or *per os* it is excreted by the liver into the gall bladder rendering it opaque to X-rays. Therefore it is largely used for diagnosis of cholecystic disease by cholecystography. For all practical purposes, oral use is

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sufficient, intravenous use is necessary only after negative results from oral use. The patient takes a light evening meal at 7 p.m., and at 10 p.m., two keratin coated gelatin capsules of 5 grs. each are taken followed by a drink of water. Every fifteen minutes two capsules are taken at a time till ten have been swallowed, accompanied by free drinks of water. In fact the patient should keep drinking water till he falls asleep. No food is given the following day. Examinations are made at 10 am., 11 a.m., and 4 p.m. At 5 p.m. the patient is given some bread and butter and another examination is made to see the effect of meal upon the shadow. For successful examination it is necessary that the drug must be absorbed and excreted by the liver, and that the hepatic and cystic ducts must be patent, as otherwise the gall bladder will not fill. It is also important that the dye must freely enter and leave the liver.

Graham's technique for intravenous use is as follows:— The injection is given early in the morning, and no food is taken except a glass of milk if hungry, although water may be drunk during the day. Three grammes are dissolved in 40 c.c. of triple distilled water and half the amount is injected slowly taking 5 to 7 minutes; half an hour later the remaining half is injected. It is necessary to wash through the needle some normal saline. Nausea and vomiting with fall of blood-pressure may occur occasionally and should be counteracted by injection of 10 ms. of adrenaline solution. 40 grs. of bicarbonate of soda in solution should be taken every three hours, day and night, as long as the patient remains awake. Radiograms are taken 3 and 6 hours after the injection. The solution must be freshly prepared.

UROSELECTAN

(Not official)

Syn.—Iodopyridon Acetate of Sodium.

Source and characters.—A greyish-white powder, soluble in water. Contains 47 p.c. of iodine in organic combination. Solution neutral.

Action and Uses

It is used intravenously to take X-ray pictures of the urinary tract in 30 grm. doses dissolved in 100 c.c. of water. The photographs are taken 15 to 20 minutes after the injection at the time of maximal excretion. As long as the kidneys are healthy and functioning normally the results are satisfactory, but dangerous in acute nephritis. About 95 p.c. of the drug appears in the urine within one and a half hours. It is non-irritating when used subcutaneously.

Uroselectan-B is supplied in sterilised ampoules ready for use. Contains 15 grms. dissolved in 20 c.c. of 18 p.c. solution of invert sugar. It is rapidly eliminated and has the advantage over the earlier preparation in that the quantity injected is less.

Abrodil. *Syn.—Sodium Iodo-methane Sulphonate; Skiodan.*—A white crystalline powder, soluble in water. Contains 52 p.c. iodine. *Used intravenously* for pyelography for the same purpose as Urose-

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lectan. Solution used is 20 G. dissolved in 100 c.c. Photographs are taken in 5 to 25 minutes. 4 p.c. solution is isotonic with the blood. About 47 p.c. is excreted in 1 hour and 90 p.c. after 10 hours.

LIPIODOL

(Not official)

Source and characters.—A compound of iodine (40 p.c.) in poppy seed oil in organic combination. In transparent, light blue oil, opaque to X-ray. Darkens by prolonged exposure to air when it should not be used.

Dose.—1 to 3 c.c. *intramuscularly* (for treatment); 5 to 20 c.c. for *diagnosis.*

Action and Uses

It has been used intramuscularly as a substitute for iodides in the treatment of asthma, syphilis and rheumatic affections. But its chief use is to visualise bronchi and their ramifications, bronchial and pleural fistulæ, permeability of bronchial fields, localisation of pulmonary cavities, and spinal cord compression. 20 to 30 c.c. is injected into trachea either through a cannula introduced through the glottis or through a curved needle inserted through the cricothyroid membrane, after anæsthetisation with cocaine. As a rule most of the drug is thrown out with the expectoration. A portion may be absorbed and excreted through the urine and saliva. When injected into the cisterna magna or into the lumbar region it helps to localise spinal cord compression. It is non-toxic and produces no reaction when given subcutaneously or intramuscularly. A case of death has recently been recorded.

Phenol Red. *Syn.*—*Phenolsulphonphthalein.*—A white, or faintly yellowish-white, crystalline powder. *Dose.*—$\frac{1}{10}$ gr. or 0.006 grm. by injection.

Uses.—It is used to test the renal function. After an intravenous injection of $\frac{1}{10}$ gr. in 1 c.c. not less than 50 p.c. for the first hour, or 75 p.c. for the first and second hours should be excreted in the urine.

GROUP XXVI

DRUGS WHOSE ACTIONS ARE MECHANICAL

Pyroxylin, Collodion, Oil of Theobroma

PYROXYLINUM

Pyroxylin

Source.—It is a nitrated cellulose, obtained by the action of a mixture of nitric and sulphuric acids on cotton wool (freed from fatty matter), and subsequent purification. Contains 11.5 to 12.3 p.c. of nitrogen.

Characters.—A white, matted mass of filaments, resembling cotton wool, but harsher to the touch. Highly inflammable.

COLLODIUM FLEXILE

Flexible Collodion

Syn.—Collodion.

Source.—Immerse pyroxylin 20 grm. in alcohol (90 p.c.) 240 mils, add 30 grm. colophony and 20 grm. castor oil, add ether q.s. to produce 1000 mils. Industrial methylated spirit may be used in place of alcohol.

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Non-official Preparations

1. **Anodyne Colloid.** *Syn.—Amyl Colloid.*—Amyl Hydride ½ oz., Aconitine 1 gr., Veratrine 6 grs., Absolute Alcohol ½ oz., Collodion to 2 ozs. Relieves pain instantly in *neuralgia, lumbago,* etc.

2. **Collodium Stypticum, B.P.C.** *Syn.—Styptic Colloid.*—Benzoin 1·5 grm., Tannic Acid 15.0 grm., Alcohol (90 p.c.) 15·0 mil., Collodion to 100 mil. A powerful *local hæmostatic.*

Pharmacology and Therapeutics

Externally.—Painted over the skin, collodion leaves a thin film from the evaporation of ether. This coating is impervious to air and moisture, and thereby causes a partial anæmia of the part by pressure on the local blood-vessels. As a *protective covering,* it may be applied to small, inflamed broken or cut surfaces, chapped nipples or threatening bed-sores. It is particularly suited to scalp wounds, as by its contractile property it not only helps to draw the edges together, but does away with the necessity of a bandage. It may be employed to arrest local hæmorrhage from small cuts or wounds, as in leech-bites, and to close punctured openings as in paracentesis. If painted over the face in small-pox it lessens pitting, and when applied to the mouth of the urethra or orifice of the prepuce it prevents nocturnal incontinence of urine in children. Mixed with salicylic acid (*see* p. 414), it dissolves corns and warts, and with salicylic acid and zinc chloride or lactic acid, small lupoid and epithelial growths. With iodoform it forms a very effective pigment for glandular swellings and with iodine for ringworm, alopecia and inflamed, gouty or rheumatic joints.

Caution.—No flame should be brought near the part until the evaporation is complete.

OLEUM THEOBROMATIS

Oil of Theobroma

Syn.—Cacao Butter: Cocoa Butter.

Source.—A solid fat expressed from the seeds of *Theobroma cocoa.*

Characters.—A yellowish-white solid fat; odour, slight, agreeable, resembling that of cocoa. Taste, bland, characteristic. Does not turn rancid on exposure to the air. Somewhat brittle, but softens at 25°C. Melts at 30° to 35°.

Composition.—Glycerides of *stearic, palmitic,* and *oleic acids.* An alkaloid, *Theobromine,* the composition of which is di-methylxanthin.

Pharmacology and Therapeutics

Because its melting point is below that of the human body oil of theobroma is used as the basis for all suppositories which are intended to dissolve slowly when introduced into the rectum.

In this country it is better to make up the suppositories as directed in the Pharmacopœia, keep them in water till required, and put them on ice to harden before they are introduced into the rectum.

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GROUP XXVII

COLOURING AND SWEETENING AGENTS

Cochineal, Soluble Saccharin, Sucrose (*see* p. 565), **Glucose** (*see* p. 566), **Dextrose** (*see* p. 566), **Lævulose** (*see* p. 568)

COCCUS

Cochineal

Syn.—Coccus Cacti. **Syn. I.V.**—*Crimidana*, *Cringdana*, Beng., Hind.

Source.—The dried female insect, *Dactylopius Coccus*, containing eggs and larvæ.

Characters.—About 3.5 to 5.5 mm. long; oval, flat, or concave beneath, convex above, transversely wrinkled; purplish-black or purplish-grey; easily powdered. Powder, dark red or puce-coloured.

Composition.—(1) *Carminic Acid*, 10 p.c. (2) *Fat*, 10 p.c. and wax 2 p.c. *Carmine* is precipitated from the decoction by sulphuric acid and other reagents.

Enters into.—Tr. Cardamomi Co., Tr. Cinchonæ Co.

Official Preparation

1. **Tinctura Cocci.**—1 in 10. **B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**

Uses.—Cochineal is used as a colouring agent. Alkalies turn carmine purple.

SACCHARINUM SOLUBILE

Soluble Saccharin

Syn.—Glusidum Solubile.

Source.—A sodium derivative of *o*-benzoic-sulphinide, and is prepared by neutralising *o*-benzoic-sulphinide with sodium hydroxide, or with sodium bicarbonate.

Characters.—A white crystalline powder, odourless, or faint, aromatic odour; intensely sweet. *Soluble* in 1.5 parts of water, in 50 parts of alcohol (95 p.c.).

B.P. Dose.—½ to 2 grs. or 0.03 to 0.12 grm.

Pharmacology and Therapeutics

In large doses, gluside is an antiseptic and passes out with the urine unaltered. It is chiefly used for its sweetening property to cover the taste of unpleasant drugs, and as a substitute for sugar in diabetes, obesity, dyspepsia, etc. Being more palatable, soluble gluside is better suited for flavouring purposes, as ordinary saccharin leaves a disagreeable after-taste.

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PART IV

VACCINE AND SERUM THERAPEUTICS

The method by which resistance is conferred upon an animal towards a given disease forms the basis of the study of immune therapy. By *immunity* is meant non-susceptibility to a given disease or a given organism either under natural conditions or under conditions experimentally produced. By *tolerance* is meant partial or limited form of immunity. Although the term is generally applied to a condition produced after repeated use of certain drugs like opium, it is now used increasingly to denote the peculiar form of partial immunity that is developed in protozoal diseases like malaria. As a result of continued infection and reinfection with the malarial parasite a condition is established in which the host is able to live a more or less healthy life and to offer some resistance to reinfection while still harbouring the parasite in small numbers. This type of infection immunity is spoken of as '*tolerance*' or '*premunition*'.

Immunity for descriptive purposes may be classified as follows :—

A. Natural Immunity.—This form of immunity is possessed by man and animal either from birth or acquired during growth by virtue of its species, racial or individual peculiarities. As an instance of *species immunity* may be mentioned the immunity of hens against tetanus, and of dogs, rats and mice against tuberculosis. The immunity of certain races to certain diseases as for example, the immunity of the negro to yellow fever is considered by some as *racial immunity*. Again some families are more resistant to certain diseases than others. Certain individuals also show varying degrees of immunity to some of the infectious diseases. In times of epidemics all persons exposed to infection do not contract the disease and even among those who develop it there are some who suffer more severely than others. Natural immunity is neither absolute nor permanent. Through the administration of large doses of infective material it is possible to break down this immunity. The immunity of the hen to tetanus for example may be overcome by giving massive doses of tetanus toxin. In the same way it is also possible to enhance natural immunity by artificial means.

B. Acquired Immunity.—Immunity may be acquired in two ways—*actively*, or *passively*. It is called *(i) active* when the individual's own tissues play an active part in the process of acquiring the resistance, and *(ii) passive* when the resistance is acquired through introduction from without, of ready-made protective substances or antibodies from other animals of the same or another species.

I. **Active Acquired Immunity.**—This again may arise *(a) naturally*, or *(b)* may be *artificially* induced.

(a) Natural Active Acquired Immunity.—It is well-known that an attack of an infectious disease confers upon a person a certain amount of immunity from a second attack. The immunity that is so developed is known as *natural active acquired immunity*. While in small-pox, measles, chicken-pox, plague and typhoid fever a high degree of immunity follows an attack of the disease; in influenza, pneumonia and gonorrhœa little or no immunity is conferred by an attack.

(b) Artificial Active Acquired Immunity.—When active immunity results from inoculation of material containing antigenic substances derived from bacteria or viruses, it is known as *artificial active immunity*. The term *vaccination* is applied to all methods of artificial active immunisation, and the material used for vaccination is known

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as *vaccine*. A vaccine may consist of *(i)* living virulent virus, *(ii)* living attenuated virus, *(iii)* dead virus, *(iv)* split products from viruses, or *(v)* toxins. Various terms are also used to denote the method of manufacture of vaccines. Thus we have *live vaccine*, in which the organism is alive and not dead; *sensitised vaccine*, which is made by mixing the organisms with specific immune serum; *autogenous vaccine*, which is made from the organism that is causing the infection in the patient; *stock vaccine*, which is made from organisms obtained from similar condition in other patients; *polyvalent vaccine*, which is made from several strains of the same organism isolated from different cases; *mixed vaccine*, which is made from two or more different organisms; *detoxicated vaccine*, which is made after removal of endotoxin of organisms; *lipo vaccine*, which is made by suspending organisms in oil instead of saline; *phylacogen*, which is made from solutions of bacterial cell bodies so as to be readily assimilable. Vaccines are generally given by injection in one or more doses at suitable intervals. Immunity is developed some days or weeks after the last injection, and is highly specific being effective only against the organisms used for the preparation of the vaccine. The degree and duration of immunity vary considerably in different cases. After small-pox vaccination it is high and lasts a considerable time (several years); after vaccination for diphtheria, scarlet fever, typhoid, cholera and plague it is moderate and lasts for several months; and after vaccination for influenza, and pneumonia it is slight and lasts a very short time only. Natural active immunity confers better and more lasting protection to an individual than artificial active immunity. The latter is of very great value in the prevention of disease and of limited value in treatment.

II. **Passive Acquired Immunity.**—If an animal is immunised by giving a series of injections of a vaccine in gradually increasing doses and at suitable intervals, its serum is found to contain protective substances or antibodies which when injected into a susceptible animal confers immunity upon it, provided the serum is given either at the time of, or a short time after, the occurrence of infection. The immunity that is thus conferred through the injection of serum containing specific antibodies from another animal is known as *passive immunity*. This immunity is of short duration and is of particular value in treatment—chiefly for tiding over a crisis when antibodies are lacking in the blood of the patient. In diseases like diphtheria, tetanus, measles and poliomyelitis, passive immunisation has not only been used for curative purposes but also in prophylaxis.

Anti-sera are of three different types. Different terms have been used to denote the nature of these anti-sera. When bacterial cell body itself is used in the manufacture of an anti-serum the antibodies elaborated are found to have the power to agglutinate, opsonise, kill, or lyse the bacterial cell. The anti-serum in this case is known as *antibacterial serum*. Examples of such serum are anti-streptococcal, anti-meningococcal and anti-plague serum. On the other hand if the filtered toxin of a bacterium is used for the manufacture of anti-serum then the protective substances present in it have the power to neutralise the toxins of the organisms only and in this case the serum is known as *antitoxic serum*. Examples of such serum are anti-diphtheritic and anti-tetanic serum. In virus diseases like measles and poliomyelitis the serum of recovered cases contain specific antibodies for the virus. Such sera have been used for passive immunisation, and are known as *convalescent sera*.

Local Immunity.—This term has recently been employed by Besredka to denote the resistance offered by tissue cells to infecting agents. In opposition to the popular view he believes that the cells of the tissue attacked are the cells primarily concerned in protection and not antibodies or phagocytes. In typhoid and dysentery the

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causative organisms attack the intestines and in anthrax the skin. If in these diseases the tissues attacked are rendered previously insusceptible then Besredka believes that the animal would behave as if completely immune. This immunity which is dependent upon the development of nonsusceptibility of tissues to the toxic action of organisms is known as *local immunity*. In connection with *local immunity* the term *antivirus* is often used. It is the name given to the material used for inducing local immunity. It is either a killed culture of the organism or a filtrate from such culture. Experimentally Besredka has shown that the application of staphylococcus or streptococcus *antivirus* to the shaved skin of rabbits confers subsequent immunity to infection with these organisms. Some therefore believe that *antivirus* has valuable curative and protective properties. Dressings soaked in *antivirus* have been used in the treatment of staphylococcal and streptococcal infections.

Bacteriophage.—In 1917 d'Herelle found that the filtrates obtained from the liquid fæces of bacillary dysentery cases, when added in small quantities to young cultures of *Bacillus dysenteriæ* (Shiga), produced lysis of the bacteria after a period of incubation. Filtrates of these lysed cultures also showed similar lytic properties. This property was not only transmissible in series indefinitely from culture to culture but was also capable of growing in strength in each culture. From this d'Herelle suggested that the lytic agent was an ultramicroscopic virus and named it *bacteriophage*. Although the majority of subsequent workers are inclined to accept this view of d'Herelle yet there are some who believe that the lytic agent is a non-living substance of the nature of enzyme. This difference of opinion has stimulated greatly the study of *phage* and has led to very fruitful results. As a consequence, we are in possession of a good deal of facts regarding the properties of *phage* and its mode of action on bacterial organisms. Briefly, the most important properties of *phage* are its filtrability, its ability to multiply in the presence of young growing bacteria, its resistance to heat and alcohol, its susceptibility to acids and alkalies, and its ability to act as an antigen. And as regards its action on organisms we know that in the presence of specific *phage* bacteria may get lysed, alter in virulence, change their cultural characteristics and become modified as regards antigenic properties. The organisms most susceptible to such action by *phage* are the members of the colon-typhoid group and the vibrios.

The value of phage so far as the clinician and the public health worker are concerned is dependent upon its therapeutic value. In diseases like cholera and dysentery the use of a specific highly potent *phage* is said to be of some value both in treatment and prevention. In India at the present time *phage* is being manufactured in several important laboratories on a large scale and is being tried extensively in the field for the cure and control of cholera. Experiments so far carried out independently in the provinces of Madras, Assam and United Provinces, have not yielded any conclusive results. All that can be said at present regarding the value of *phage* in cholera is (i) that in prophylaxis there is some evidence that administration of *phage* helps to reduce mortality though not morbidity, and (ii) that in treatment giving of *phage* is better than giving no treatment, but it is not better than giving other recognised forms of treatment.

The production of *artificial immunity* is what we are mainly concerned with in this section, and will be discussed under two sections.

A. Serum Therapy, or passive artificial immunisation.

B. Vaccine Therapy, or active artificial immunisation.

Antigens.—When any foreign protein substance is injected into an animal either subcutaneously or intravenously, the tissue cells react against these poisons and produce specific antibodies. These foreign

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protein substances are collectively known as *antigens*. The antigens that concern us are the toxic protein substances of pathogenic bacteria and are more usually called toxins.

Bacterial toxins may be (*a*) *exotoxins*, *i.e.*, poisons that are given off by the bacteria into the liquid culture media; they are entirely separate from the bodies of the bacteria and can be obtained in the broth after filtration; (*b*) *endotoxins*, *i.e.*, poisons that are intracellular and incorporated with the other proteins in the body of the bacteria.

The diffusibility of the exotoxin into the culture media has an important bearing on the production of specific sera. The soluble exotoxin can be separated, injected into animals, and after a time the serum of the animals contains a definite specific body—"The Antitoxin." To this group belong the antitoxins of diphtheria, tetanus, botulinus, etc.

In the case of bacteria that only produce endotoxins, the whole organism must be injected into an animal in order to immunise it. The bacteria are broken down by the tissues, and the endotoxin is liberated, a much weaker antiserum is produced, which has a lytic action on the particular bacteria used—this serum is known as a "Antibacterial Serum." To this group belong the bactericidal sera against the streptococci, B. coli, anthrax, etc.

A third group of organisms form a certain amount of soluble exotoxin as well as possessing powerful endotoxins, so that animals injected with unfiltered broth cultures produce serum which is partly antitoxic and partly bactericidal, *e.g.*, dysenteric and meningococcal anti-sera.

Specific antibodies.—When soluble proteins are injected into animals, a definite anti-serum is formed; the antisubstance is found to be mainly in the globulin fraction of the serum. These globulins are capable of neutralising the poisonous soluble proteins and rendering them harmless to the animal. The neutralisation may be effected as follows:—

(*a*) *Antitoxin Serum.*—By the globulin fraction of the anti-serum combining with the toxin and increasing the size of the molecule without any marked alteration in the electrolytic charge of the two phases of solvent and solute. The union is a loose one and the toxin can be separated from the antitoxin by dialysis.

(*b*) *Precipitin Serum.*—By denaturalising the foreign albumins from an emulsoid into a suspensoid state, and at the same time causing an alteration in the electrolytic charge of the solution. This causes coagulation which in most cases is irreversible.

When insoluble substances, *e.g.* bacterial suspensions, red blood-cells, etc., are injected into an animal, the tissues respond differently as they have to break down masses of foreign proteins instead of dealing with proteins in solution (exotoxins, etc.). Such masses must be broken down by the enzyme action of the fixed connective tissue cells and leucocytes into soluble products as the result of their digestive action. The different stages of this digestive enzyme are shown in the serum in the following ways:—

A. *Bactericidal Action.*—This action is compared to that shown by the various enzymes in breaking down the natural proteins from an emulsoid state into metaproteins, etc., in a suspensoid state. Thus leading to:—

(1) Death of the bacteria by digestion of the natural proteins as shown by bactericidal sera.

(2) The slowing of the movement that precedes death, and the alteration of the viscosity of the plant cell as the result of digestion. The bacteria tend to clump together owing to Brownian movement and increased viscosity, as shown by agglutinins.

(3) Finally the bacteria are killed and completely dissolved into still lower proteins—"The Bacteriolysins."

B. Wright considers that after artificial immunisation by bacterial

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emulsions certain substances are formed in the blood—"opsonins"—which increase the avidity of the polymorphoneuclear leucocytes, and so help in resisting the invasion of the tissues by bacteria.

An enzyme requires the presence of a coenzyme to digest proteins so does the analogous amboceptor; immune body or bacteriolysin requires the presence of a complement or alexin to digest bacteria, cells, etc. Most of the bactericidal sera may be regarded as sera containing specific enzymes for the particular bacteria. The delicate nature of most enzymes to temperature, violent shaking, etc., offers a possible explanation to the small value these bactericidal sera have in practice.

Specific diagnosis.—In the successful treatment of a case by vaccine or serum therapy it is essential to find the causative organism or organisms of the disease. The isolated organism, if it happens to be one that forms exotoxins enables us to employ antitoxic serum as early as possible, or if one that only forms endotoxins, the bacilli can then be killed and employed as a vaccine for the immunisation of the patient from whom they were cultivated. Various methods may be employed in determining the specific organism, *viz.*—

(1) The organism can be cultivated from the tissues and identified by the various bacteriological methods. This is the only sure and safe method.

(2) The detection of certain specific bodies produced in the host by the causative organism, *e.g.* (*a*) *the determination of antibodies*, specific agglutinins, as in the well-known Widal test; (*b*) *the determination of specific bacteriolysins.* The estimation of the agglutination depends on knowing the normal agglutinating power of the blood, that of persons inoculated, and the correct appreciation of the existence of coagglutinins in closely allied infections, *e.g.* the typhoid coagglutinin in paratyphoid fever.

(3) Certain non-specific tests, (i) the determination of complement deviating bodies as in the Wasserman's reaction, the cobra venom and platinum chloride tests for syphilis, (ii) in certain diseases a very definite blood picture is given by estimating the number and variety of the leucocytes present in circulating blood.

The above mentioned tests are given in order to insist that the recognition of the specific organism is the only sure test, and the employment of it is an essential preliminary before the employment of serum or vaccine therapy; full details for doing them will be found in the various text-books on bacteriology. A considerable amount of knowledge and experience is necessary to obtain reliable results by these methods. Unless the physician possesses this knowledge and the facilities for doing these tests, it is better in the interest of his patient to advise that a specialist be called in to make the necessary examination.

A diagnosis having been made as to the causative organism, the next step is to apply the treatment necessary for the case. A just appreciation between the value of a given drug or vaccine must be made in every case, thus in impetigo contagiosa the specificity of Unguentum Hydrargyri Ammoniati renders vaccine treatment unnecessary, whilst the employment of calx sulphurata is not justifiable in folliculitis due to staphylococcus without using vaccine therapy; again in the dysentery due to Shiga's bacillus, the early use of antitoxic serum with magnesium sulphate is the only legitimate treatment to adopt.

The defensive substances formed in the body are to a large extent specific for each organism. Thus the antitoxin formed against diphtheria will neutralise only diphtheria toxin, and so forth. The blood which is bactericidal for typhoid bacilli will have no effect on, say, plague bacilli.

In the treatment of bacterial diseases either with serum or vaccine, the aim is to assist the natural forces of the body in their struggle

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with the invading organism, either by supplying substances which will neutralise the poisons of the invader (antitoxin), or by stimulating the cells of the body, not engaged in the struggle, to manufacture antibodies. This method of treating infectious diseases is known as *specific therapy*.

Method of administration :—

(*a*) *Subcutaneously.*—This is the common route and is usually adopted, the best site being the loose cellular tissue of the flank or the lower abdomen, or the thigh under the fascia lata. The usual cleanliness having been done the needle is inserted by stretching the skin. When a large quantity is to be given, it may be injected on either side of the flank. The part is then covered with a little cotton wool soaked in collodion or Friar's balsam.

(*b*) *Intravenously.*—This route is taken in bad cases specially when the injection has been delayed. Under proper aseptic conditions there is very little risk, the serum should be diluted with three times its volume of normal saline.

(*c*) *Per rectum.*—This is done only when there is any objection to subcutaneous route. First wash out the rectum, and the serum diluted with normal saline to make the total bulk not less than 100 c.c. is slowly introduced into the rectum. The utility of giving serum by this route is doubtful.

(*d*) *Oral* route is sometimes recommended, although it is open to doubt whether this route is of any value except when local action in the stomach is aimed at, as for instance in the treatment of gastric or duodenal ulcer. Some sera are capable of producing specific effect when given by this route, specially diphtheria antitoxin. It should be diluted to at least 50 c.c. in bulk with normal saline and given on empty stomach.

(*e*) *Intrathecally.*—This route is used in the treatment of cerebro-spinal fever, meningeal infections and tetanus. After making a lumbar puncture, an amount of cerebro-spinal fluid equal to the bulk of serum to be injected is first drawn out, the serum is then allowed to flow by gravity from a height of 9 to 12 inches, or injected very slowly. In either case the serum should be warmed to body temperature. It is desirable to give these injections under general anæsthesia.

A. SERUM THERAPY

Under this head come the various methods by which we endeavour to cure a patient of a given disease by injecting him with the blood serum of an animal that has attained a high degree of active immunity either against the organism which is the cause of the particular disease, or against the toxin of the organism.

(*a*) Antitoxic Sera :—

The best example of antitoxic sera are diphtheria and tetanus antitoxins. Before describing these in detail it is necessary to explain how an antitoxic serum is prepared. The steps in the process are :—

(1) The preparation of a powerful toxin.
(2) The gradual immunisation of an animal against the toxin.
(3) The estimation of the antitoxic power of the serum of the animal thus treated.

It is not necessary to go into the details of the manufacture of the toxin. All that need be explained is that the power of the toxin is estimated by finding out what is the smallest amount that will with certainty kill a guinea pig of 250 to 270 grms. within five days. This is called "the minimum lethal dose" or M.L.D.

A large animal (usually a horse is used) is gradually immunised by the injection of increasing doses of this toxin. When a high degree of immunity is considered to have been attained, as the animal can now stand larger doses of the toxin, the antitoxic power of its serum is

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tested by mixing varying quantities of serum with a fixed amount of toxin, and is expressed in immunity units.

(1) In all cases the serum ought to be injected as early as possible, and in large doses, because the antitoxic molecule does not dialyse readily through the endothelial walls of the finer capillaries, whilst the toxin molecule can do so owing to its smaller molecular form. Hence if the central nervous cells are attacked by the toxin, the antitoxin cannot penetrate into this area to displace the toxins. Even very large doses are without harmful effects beyond the occasional production of urticarial and erythematous eruptions.

(2) Where large doses of serum are necessary, injections must be made at different parts of the body: not more than 20 c.c. should be injected at one place.

ANTITOXINUM DIPHTHERICUM, B.P.

Diphtheria Antitoxin

Source.—A serum, or a preparation from serum, containing the antitoxic globulins, which have the specific power of neutralising the toxin formed by *Corynebacterium diphtheriæ*. Prepared by separating the serum from the blood of animals, which have been immunised by graded injections of sterile filtrate from a culture of *Corynebacterium diphtheriæ* on a fluid medium. May be used in the liquid form or may be dried. These are distributed in sterile glass containers sealed to exclude bacteria. The antitoxic globulins may be obtained from the serum by fractional precipitation, and the precipitate may be used either in solution, or dried.

Characters.—The serum is yellow or yellowish-brown. The antitoxic globulin solution is yellowish-brown or greenish-yellow. Both liquid forms are initially transparent, becoming opalescent in time. Almost odourless, with faint odour of the antiseptic. Solid forms are yellowish-white powder, or yellowish-brown flakes, and resemble liquid forms when dissolved in 10 parts of water.

B. P. Dose.—500 to 1000 Units (Prophylactic); or **10,000 to 20,000 Units** (Therapeutic) by injection.

TOXINUM DIPHTHERICUM DIAGNOSTICUM, B.P.

Schick Test Toxin

Source.—Used for the diagnosis of susceptibility to diphtheria. Obtained by preparing a sterile filtrate from a culture on nutrient broth of *Corynebacterium diphtheriæ* which, after being allowed to mature is diluted before use so that 0.2 mil contains the test dose. The sterile filtrate may be diluted with a sterile solution of sodium chloride to make it isotonic with blood. It is distributed in diluted and undiluted forms in sterile containers.

B.P. Dose.—(By intradermal injection) **0.2 mil or 3 ms.**

TOXINUM DIPHTHERICUM CALEFACTUM, B.P.

Schick Control

This is *Schick Test Toxin* heated at temperature not less than 70° for not less than five minutes. It is prepared from the same batch of Schick Test Toxin as that with which it is issued for use.

B.P. Dose.—(By intradermal injection) **0.2 mil or 3 ms.**

TOXINUM DIPHTHERICUM DETOXICATUM, B.P.

Diphtheria Prophylactic

It is the sterile filtrate, or material derived from a filtrate, of a culture on nutrient broth of *Corynebacterium diphtheriæ*. It occurs in the following forms:—

(a) **Diphtheria Toxin-Antitoxin Mixture,** prepared by adding diphtheria antitoxin to the filtrate.

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(b) **Diphtheria Toxoid, or Anatoxin,** prepared by treating the filtrate with formaldehyde.

(c) **Diphtheria Toxoid-Antitoxin Mixture,** prepared by treating the filtrate with formaldehyde, and adding a small quantity of diphtheria antitoxin.

(d) **Diphtheria Toxin-Antitoxin Floccules,** prepared by adding diphtheria antitoxin to the filtrate in the proportion necessary to produce a suitable flocculation, separating the floccules, and washing and suspending in normal salt solution.

(e) **Diphtheria Toxoid-Antitoxin Floccules,** prepared by treating the filtrate with formaldehyde, adding diphtheria antitoxin in the proportion necessary to produce a suitable flocculation, separating the floccules, and washing and suspending them in normal salt solution.

Distributed in sterile containers.

B.P. Dose.—(By subcutaneous injection). The volume indicated on the label as the dose, on two or three occasions, at intervals of two to four weeks.

Action and Uses

Diphtheria antitoxin is used as a specific in the treatment of diphtheria. It neutralises the toxin elaborated by *C. diphtheriæ* locally at the seat of the disease, but does not affect the vitality of the infecting organisms. The dose which was originally recommended was 1500 units; the amount required as an initial dose increases with the lapse of time from onset of disease to the time of injection. If the case is not treated until the second day, give 4000 to 8000 units; till the third day, 8000 to 12,000 units. In all cases when the larynx is involved, the initial doses should be at least 6000 units and similarly 8000 units if nasal symptoms are present. The dose may be repeated in 6 to 24 hours. Each millilitre contains 400 units, and if there is any objection to using such a large quantity then a concentrated high potency serum should be selected which contains 2500 units or more per millilitre. The serum should always be administered as early as possible; indeed it is of less value unless given within the first 48 hours of the disease. For this reason in all cases of suspected diphtheria it is well to inject the antitoxin at once without waiting for a bacteriological report; even if the case be not one of diphtheria no harm can result. Another point to remember is that diphtheria is a much more fatal disease in children than in adults, and requires if anything larger doses of antitoxin. *Do not make the mistake of reducing the dose of antitoxin in proportion to the age of the patient.*

The proper place for injection is in the flank or between the shoulder blades.

Preventive Inoculation.—Diphtheria antitoxin has been employed to confer immunity in persons exposed to diphtheria. The usual dose is 500 units irrespective of age. This gives protection after 24 hours and lasts for about three weeks. It has the disadvantage of rendering the patient hypersensitive to subsequent injections of serum (*see* Anaphylaxis, page 645). But a more lasting immunity is afforded by the injection of the special diphtheria prophylactic, which,

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as described above, consists of five different kinds in which the toxin has been made harmless either by combining with antitoxin or modified to toxoid. These may be used in preference to the antitoxin serum. The immunising power of the *toxin-antitoxin mixture* depends on the amount of the toxin and toxoid which has not been neutralised by the antitoxin, although it is possible that some of the bound toxin and toxoid is also set free. *Anatoxin* or *toxoid* occasionally produces inflammatory reaction at the site of injection, therefore it has not been extensively used. But the *toxoid-antitoxin mixture* is free from this reaction. *Toxin-antitoxin floccules* when injected provoke antitoxin formation possibly due to slow dissociation of the floccules into their constituent parts. It causes no inflammation at the site of injection. A further improvement is the *toxoid-antitoxin floccules*, and are the best form of diphtheria prophylactic at present available. The usual dose is 1 mil (15 ms.) given subcutaneously, followed three weeks later by a second dose of the same amount, and one or two weeks later by a third dose of 1 mil. It takes about one to six months to develop immunity, but once developed it will last for more than six years. This inoculation is not given in the presence of actual diphtheria where immediate protection is needed, but is used in schools, asylums, hospitals, orphanages, etc., to protect against possible outbreaks.

As a rule the injections are given after testing the patient's susceptibility to infection with Schick test toxin. This is done by injecting intradermally 3 ms. (0.2 mil) of toxin on the forearm, and since the skin reaction may be due either to the specific toxin, or to non-specific substances present, a control test is made on the opposite arm with the Schick control in order to exclude reactions due to non-specific substances. A positive reaction indicates that the individual is susceptible to diphtheria, and this is shown by the appearance within twenty-four to thirty-six hours of a circumscribed area of red flush. A negative reaction indicates that the subject is immune to diphtheria and is shown by the absence of reaction in the arm.

ANTITOXINUM TETANICUM, B.P.

Tetanus Antitoxin

It is a serum, or a preparation of serum, containing the antitoxic globulins, which have the specific power of neutralising the toxin formed by *Bacillus Tetani*. Prepared by the same way as diphtheria antitoxin, except that the animal is immunised with a culture of *B. Tetani*.

Characters.—The same as diphtheria antitoxin.

B. P. Dose.—**1000 to 2000 Units** (Prophylactic); or **20,000 to 40,000 Units** (Therapeutic) by injection.

Action and Uses

The main use of antitetanic serum is for the **prevention of tetanus** following contused and lacerated wounds. For

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this purpose 1000 to 3000 units are injected as soon as possible and if the wound is extensive and badly lacerated a second injection is given within 1 to 5 days. This serum when used for prophylactic purposes should contain not less than 300 units (=150 American units) per mil. The dried material must not contain less than 3000 units per grm. When the serum is used for curative purposes the potency must not be less than 1600 units per mil, and solid preparations of not less than 16,000 units per gramme. The tetanus bacillus usually grows in the wound only for the first few days after injury, and it is during this short space of time that most of the toxin is elaborated and reaches the central nervous system. Once the symptoms of tetanus have developed, it means that the toxin has reached the nerve cells in the brain and spinal cord. The antitoxin molecule is too large to dialyse through the vessel walls into cerebro-spinal fluid. The serum must therefore be introduced partly *intrathecally* and partly intravenously, the dose being 20,000 units to be repeated on two successive days if necessary. Even larger doses (80,000 to 200,000) have been recommended *intravenously*, which prevent further toxin from the wound reaching the central nervous system. It stands to reason that subcutaneous injection of small doses is useless to cure tetanus. When combined with intravenous injection of hexamine it gives better results (*see* page 386).

ANTITOXINUM WELCHICUM, B. P.

Gas-gangrene Antitoxin (perfringens)

It is a serum, or a preparation from serum, containing the antitoxic globulins, which have the specific power of neutralising the toxin formed by *Bacillus perfringens (Bacillus Welchii)*.

Prepared in the same way as other serum, except that the animal is immunised with culture of *Bacillus perfringens (B. Welchii)*. Characters are the same as other sera.

B. P. Dose.—4,000 Units by injection (Prophylactic); or **10,000 to 20,000 Units** intravenously (Therapeutic).

Action and Uses

Gas-gangrene is a gangrene of the body tissues caused by the gas-producing bacterium. In severe forms the tissue when pressed crepitates from the liberation of gas inside. Infection with this organism is the cause of peritonitis and intestinal paralysis which follow abdominal operations; therefore it is used as a prophylactic in acute intestinal obstruction and in acute peritonitis with obstruction when 4000 units are injected before operation intravenously, followed by intramuscular injections of smaller doses. Larger doses (10,000 units) are used for curative purposes intravenously, followed by smaller doses until the bowels act regularly.

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SERUM ANTIDYSENTERICUM (SHIGA), B. P.

Anti-dysentery Serum (Shiga)

It is a serum, or a preparation of serum, containing the immune substances, which have a specific value, when injected into persons infected by *Bacillus dysenteriæ* (Shiga).

It is prepared in the same way and has the same characters as other similar sera, except that the animals are immunised with cultures of the *B. dysenteriæ*.

B. P. Dose.—4,000 to 10,000 Units (by injection).

Action and Uses

Its early use improves the outlook of bacillary dysentery and whenever possible it should be given intravenously after first testing the sensitiveness of the patient with $\frac{1}{3}$ to 2 c.c. of the serum given subcutaneously twelve hours before the large intravenous dose. Shiga claims that by its use he has reduced the mortality from bacillary dysentery in Japan from 35 p.c. to 9 p.c. This was certainly the general experience during the war. The dose is 20 c.c. and should be given if possible within the first 24 hours of the disease; after 48 hours it has little curative value. It is important to use a polyvalent serum as there are various strains of this bacillus. Ordinarily 1 c.c. is equal to 1000 units, and the most potent preparation contains as much as 5000 units per c.c.

SERUM ANTIMENINGOCOCCICUM, B.P.C.

Anti-meningococcus Serum

It is a serum obtained from the blood of horses which have been immunised against strains of the meningococcus *(Diplococcus intracellularis meningitidis* Weichselbaum or *Neisseria meningitidis)*, isolated from different sources. Four serological types of the meningococcus are known, viz. type I, II, III and IV, and the serum is prepared by immunising the horses to all four types. The serum is a polyvalent serum. Group I corresponds to types I and III, and Group II, types II and IV.

Dose.—10 to 30 mils by intrathecal or intravenous injection.

Action and Uses

The serum ordinarily in use is a polyvalent one prepared against a number of strains belonging to the different types of meningococci. During an epidemic period the strains isolated usually belong to types I and III (Group I) and when the type of the organism isolated from a case can be determined, and it belongs to either of these, a Group I serum may be used. The serum should be injected both intrathecally and intravenously. In giving injections by lumbar puncture the cerebro-spinal fluid escaping under pressure should be measured and replaced by a smaller quantity of serum. The serum should be warmed to body temperature by immersion in water at 100°F. and at least 30 c.c. given if possible. The injection should be repeated according to the gravity of the case, and may be required at intervals of 12 to 24 hours. Intravenous injection of 20 c.c. to 50 c.c. should also be employed as early as possible. Both concentrated and unconcentrated sera are prepared. No accurate method of standardisation is available for anti-meningococcus serum.

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Ferry's Antitoxic Serum.—This serum, prepared by the use of the filterable toxin of the meningococcus obtained from young bouillon cultures, is at present under trial. The serum is standardised and is considered to have a high antitoxic value. As in the case of the other antimeningococcal serum the best results have been obtained by it when used at the earliest stage of the disease.

(*b*) **Antibacterial Sera**:—

In the preparation of these sera the immunisation has been carried out by the injection of living or dead bacteria which are the cause of the disease against which it is wished to secure protection. They are not antitoxic but they are bactericidal. In addition to this there is one very important difference between antitoxic and antibacterial sera. This difference is that whereas in antitoxic sera the actual substance which neutralises the toxin is of the nature of a chemical antidote, the bactericidal effects of the antibacterial sera require the presence of two distinct substances which are called the "immune body" and the "complement." The immune body is only developed in the serum after the injection of bacteria, but once developed it is fairly stable. The complement on the other hand is present in normal serum in a small quantity but it is easily destroyed by heat, and it rapidly disappears from the serum after withdrawal from the body. The complement appears to be of the nature of a ferment and it is probable that it is the actual bactericidal agent, whilst the "immune body" is merely the connecting link between it and the bacterium upon which it acts.

Be that as it may, there can be no doubt of the following facts:—

1. In order that an antibacterial serum may be of any use the presence of both "immune body" and "complement" is necessary.
2. The "complement" rapidly disappears from the serum after it has been withdrawn from the body.
3. The "complement" which exists naturally in human blood serum does not appear to act in conjunction with the "immune body" contained in the serum of the horse.

The practical result is that all these sera must be fresh, and to prevent deterioration they are kept in an ice chamber. They were largely manufactured by various chemical firms with the hope that because the diphtheria antitoxin had a distinct curative effect, that every other bacteria whether they produced an exotoxin or not, should give similar results.

Sclavo's Serum for Anthrax.—This is an anti-bacterial serum prepared by immunising a horse against the *Bacillus anthracis*. The dose of the serum recommended in ordinary cases is 30 to 40 c.c. subdivided into three or four injections subcutaneously into different parts of the abdomen, and followed in 24 hours, if necessary, by further injections of from 20 to 30 c.c. In grave cases the injection should be intravenous, preferably into one of the superficial veins on the back of the hand. The dose in this case should be 10 c.c. followed in an hour or two, where there is no improvement, by another similar dose.

In an ordinary case of malignant pustule, such as is seen in those dealing with hides, if seen at an early stage, a single injection may be sufficient to effect a complete cure with very little loss of substance.

SERUM ANTIPNEUMOCOCCICUM, B.P.C.

Anti-pneumococcus Serum

It is a serum, or preparation of serum, containing the immunising substances which have a specific neutralising effect on pneumococci. Four serological types of *Diplococcus pneumoniæ* are recognised, but the potent antiserum can be prepared from types I and II only. The globulins containing the specific protect-

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ive substances may be obtained from the serum by fractional precipitation and are used in solution, the product is known as *Felton's Antipneumococcus Serum.* The serum is standardised, the unit being the amount that will protect a mouse against a million fatal dose of pneumococcal culture.

Dose.—10,000 or 20,000 units by injection.

Action and Uses

The discovery of serological types of pneumococci have amply demonstrated why early attempts to produce an effective serum failed, and also showed that the problem was complicated by the fact that each type required its own specific serum. The pneumococcus produces a specific soluble antigen which accumulates in the blood in large quantities, and the object of serum treatment is to raise the concentration of the antibody to an adequate level. For this end the antigen already present must be neutralised, and it is therefore necessary to inject early and in large doses. The serum is not antitoxic but bactericidal, and aids phagocytosis.

This serum contains antibody to type I and to a less extent to type II pneumococcus. The effects in cases of primary pneumonia are shown by a rapid fall of temperature and progressive disappearance of all signs of toxæmia. The cyanosis disappears after the first or second dose which is very characteristic, and the viscid, blood-stained, rusty sputum changes to a lose, purulent expectoration.

The best results are obtained if the treatment is started early. The first dose is 10,000 units of type I and of type II antibody. As long as the temperature remains high, or in the presence of toxæmia, the injections are repeated every eight to twelve hours. Some recommend larger doses, *viz.* 40,000 to 50,000 units in moderately severe cases, and double the amount in severe cases in the first twenty-four hours. When the case is typed, a monovalent serum may be given. If due to type IV do not give the injection after the third dose, as the antibody for these strains are so feeble that it will be of little use. Subsequent injections depend upon the condition of the patient. The serum is expensive, and if it is to be used economically the type of infection should be determined, which is not so easily possible for patients treated in their own homes. There may therefore be considerable delay which means the administration of larger doses.

It is best given intravenously, and repeated injections require considerable dexterity, specially in children.

Unpleasant symptoms such as rigors, anaphylactic shock, and respiratory distress may occur, but these should not prevent its administration as they are usually relieved by an injection of adrenaline. It is however inadvisable to inject the serum into subjects suffering from allergic conditions, *e.g.* asthmatics, or into elderly persons with arterio-sclerosis.*

It has also been used in primary pneumococcal meningitis and primary pneumococcal peritonitis.

Antistreptococcic serum.—It is a polyvalent serum used in different streptococcal infections, but the results are not very encouraging owing to the fact that the complement disappears very soon. Fresh serums, if available, can be used with some success in puerperal sepsis, erysipelas, and other streptococcal infections.

Besides these antibacterial sera, serums have been prepared, against Staphylococcus, B. coli, Gonococci, etc., but they have not stood the test of time.

Anti-venom sera.—Sera which are capable of neutralising the toxic action of the venoms of poisonous snakes are prepared in different parts of the world against the venoms of local species. The Pasteur

*W. H. Wynn, *British Medical Journal,* Jan. 11. 1936

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Institute, Paris, prepares four kinds for use against the venoms of snakes occurring in Europe, Africa (2) and India and Egypt.

Other anti-venom sera are prepared in India, South Africa, Australia, South America and other countries for local use.

The principle of their preparation is the same as in the case of other antitoxic sera, horses being immunised by the injection of progressive doses of solutions of the dried snake venom instead of filtered bacterial toxins. Anti-venom sera are standardised accurately by determining the amount of serum required to neutralise a given quantity of venom when a mixture of the two is injected into test animals.

Dose.—100 mils or more, intravenously.

Kasauli Antivenene.—This serum is prepared against the venoms of the Indian Cobra *(Naja tripudians)* and the Daboia *(Vipera Russellii)*. The preparation issued is a solution of the pseudoglobulin fraction of the serum which contains all the effective antitoxin and represents a four-fold concentration of the original serum. The antivenene is preserved by the addition 0.35 per cent tricresol and retains its potency for two years. Phials of 10 c.c. are issued and it is standardised to neutralise at least 2 mg. of cobra venom and 4 mg. of daboia venom per cubic centimetre.

The contents of one or two phials should be injected in the case of daboia bite and two or more in the case of cobra bite. The injections should be repeated if the symptoms do not rapidly improve. Injections should always be given intravenously when possible as the antivenene is several times more effective by this route than when given subcutaneously or intramuscularly.

NORMAL SERUM

Antilytic Serum

It is generally prepared from the blood of healthy horse or sheep. The blood is first withdrawn and allowed to clot and when the serum separates it is collected and a small quantity of preservative (generally cresol) added. Finally it is tested to determine its hæmolytic and toxic properties, and bacteriologically examined for sterility.

It contains serum globulins, serum albumin, fibrin ferment and the natural salts of the blood.

Dose.—10 to 20 c.c.

Action and Uses

Owing to the presence of antitrypsin, which neutralises the proteolytic ferments of pus, normal horse serum is used as a local application to promote healing of old wounds and chronic ulcers. As it contains fibrin ferment it helps **coagulation of blood**, and is largely used as a **hæmostatic** in internal hæmorrhages, *e.g.* **hæmophilia**, which is believed to be due to deficiency of thrombokinase in the blood, **purpura** and in **gastric** and **duodenal ulcers** with hæmorrhage. It is given orally and subcutaneously in **anæmia**, and in **debility** due to chronic diseases.

Anaphylaxis

It has been observed that if an animal is injected subcutaneously or intravenously with some foreign soluble protein, whether toxic or not, it produces no symptoms at all, but a subsequent injection of the same protein, after an interval of 2 to 14 days, produces a rapid and even fatal poisoning. This reaction is specific for each protein, *i.e.*, if the first injection consisted of horse serum, any other animal serum will have little or no reaction. This phenomenon is known as "anaphylactic shock," and resembles those produced by the injection of peptone, or histamine. These poisoning symptoms are of

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the same type no matter what protein substance is given. The symptoms are a fall of temperature, constriction of bronchial muscles as evidenced by pulmonary distress and asphyxia, fall of blood-pressure from relaxation of the capillaries, local urticarial reactions, stimulation of the smooth muscles, *e.g.* stomach, intestine and uterus, and diminished coagulability of the blood. The severity of the symptoms varies in different persons and the symptoms usually pass off in the course of an hour or two. A few fatal cases have been recorded.

The term anaphylaxis was originally used to explain a condition opposite to immunity, but it is now used to designate all artificially induced conditions of hypersensitiveness in man and lower animals.

Various theories have been advanced to explain the cause of this anaphylactic reaction. Friedberger suggested that the antigen combined with the antibody giving rise to precipitin, which by combining with the alexin circulating in the blood formed *anaphylotoxin*, the cause of anaphylactic phenomena. Others again believe that the reaction is due to disturbance of the delicately adjusted colloid balance of the blood producing deposits of fibrin. Vaughan and Wheeler argue that the first injection causes a modification of the proteins introduced by enzymes, which leads to the development of a larger amount of ferment-like bodies which are capable of splitting protein rapidly, with the result that subsequent injections are followed by liberation of toxic substances more quickly from the decomposition of proteins giving rise to these symptoms. Dale and Laidlaw pointed out that an injection of histamine into guinea-pigs produced symptoms similar to those of anaphylaxis, though not identical. According to them the first injection helps the formation of a new antagonistic body *precipitin*, which penetrates the cells of unstriated muscles and other tissues, with the second injection the protein (antigen) penetrating into the cells reacts with the precipitin producing the typical symptoms.

The best example of anaphylaxis in man is the symptom-complex observed when a second injection of the same serum is given after eight to ten days of the first injection. These symptoms are produced not from any 'anti' substance contained in the serum, but as the result of the introduction into the human system of the foreign proteins contained in the horse serum. Anaphylaxis is of considerable importance in serum treatment, *e.g.* a patient who had a previous course of serum and has to be treated with it again. In case there is suspicion that the sensitive state exists, a preliminary injection of 0.1 c.c. of horse serum or the serum to be used is given intradermally, if no reaction follows within one hour, the patient is nonsensitive.

Allergy or *hypersensitiveness* is the unnatural or exaggerated susceptibility to a substance which is harmless in similar amounts to the majority of the members of the same species. Allergy differs from anaphylaxis in that the reaction does not usually desensitise. Examples of allergy are the various food idiosyncrasies, *e.g.* appearance of urticaria, some forms of hay fever, many cases of spasmodic asthma. The nature of sensitisation may be determined in some cases by performing cutaneous inoculation with a series of protein solutions (*see* Protein Therapy 657).

After-effects of Sera.—Administration of sterile normal horse-serum even for the first time, sometimes gives rise to various clinical manifestations commonly known as *serum sickness*. The usual symptoms are cutaneous rashes, fever, œdema and joint pains. These generally appear between eight and fourteen days, and are avoided by the use of calcium. A concentrated serum is not likely to produce these symptoms as whole serum, due possibly to the smaller dose of the former. Serum sickness is also a form of anaphylactic phenomenon, although it is customary to call the severe, fatal and rare instances of death following the use of serum as anaphylaxis.

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Treatment of Serum Disease.—This may be either for the prevention of anaphylactic shock or to combat the symptoms when the manifestations have, inspite of the precautions taken, appeared.

Prophylactic Treatment.—1. Calcium in the form of chloride, gluconate or lactate should be given after all therapeutic serum injections in 10 to 15 gr. doses, three or four times a day. Adrenaline (5 to 8 ms.) is always useful and may be combined with the serum, or atropine may be used.

2. The second injection may be rendered harmless by diluting it with normal saline solution in the proportion of 1 in 10.

3. *Besredka's Method of Anti-anaphylactic Vaccination.*—This consists of giving injections of small amounts of the serum before the massive injection.

Curative Treatment.—The patient should receive a purgative and kept on milk diet for a few days. If the symptoms are sudden and urgent, 4 to 6 c.c. of *ether* should be given intramuscularly, followed by the administration of *calcium* either by the mouth or as injection. *Atropine* hypodermically followed by *adrenaline.* These reactions are also controlled by oral use of pancreatin, and combined administration of sodium benzoate and salicylate.

B. VACCINE THERAPY

A *vaccine* is a sterilised suspension of organisms, living or dead, in normal saline, which when injected into a man or animal provokes formation of immunity or antibody which directly or indirectly either destroys the infecting organisms or neutralises the toxin produced by these organisms. Vaccines may be used for the purpose of (i) *preventing disease* (prophylactic vaccines), or (ii) *curing the disease.* The vaccines are essentially the same in both cases (*i.e.*, bacillary emulsions), the object being to stimulate the protective mechanism of the body to form anti-substances against the particular organism and so resist the disease. The vaccines may be prepared from the specific organism of the disease (specific vaccines), or an organism may be used which does not cause the specific disease, *e.g.* a staphylococcus vaccine in the cure of simple parenchymatous goitre, which acts probably by stimulating the general defensive mechanism (non-specific vaccines).

(1) *Specific Vaccines* :—

Selection of the Organism for the Preparation of the Vaccine.—Vaccines are known as (*a*) *autogenous*, when the organism is isolated from the patient's diseased tissue, grown in pure cultures and a vaccine prepared from these pure cultures; (*b*) *stock*, when the causative organism is diagnosed clinically and the vaccine prepared from a stock laboratory culture. As a general rule autogenous vaccines give the best results, but usually some delay occurs in their preparation, in such cases it may be desirable to start the treatment with a stock vaccine.

Methods of Preparation of Vaccines.—The organism is grown on solid medium for twenty-four hours. It is then emulsified in normal saline, *i.e.*, 0.85 p.c. sodium chloride solution is added to the growth; this is carefully rubbed off with a sterile bent glass rod and emulsified. The emulsion is removed by a sterile pipette to a sterile test tube or small flask and repeatedly shaken to insure the breaking up of any clumps. The bacteria are now killed. This is done by heat at 60°C. for 10 minutes, or 0.5 p.c. carbolic acid for 24 hours.

The tubes or flasks are immersed in a water-bath, which should have a cover and kept at a fixed temperature for about 10 minutes. The thermal death point of different organisms varies. In making the vaccine the temperature of the bath should be just above the death point of the organism, because if subjected to too high a

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temperature the antigenic properties of the vaccine may be impaired. For the B. typhosus, 56° to 58°C. is sufficient. The bacteria may be killed also by chemical agents, *e.g.* 0.5 p.c. carbolic acid is added and the vaccine is incubated for 24 hours. In any case after killing by heat a preservative is added, generally 0.5 p.c. phenol or cresol. The sterility of the vaccine is then tested. When the organism is grown on fluid medium no emulsification is required. The period of the growth of the organism in the fluid medium varies. The flask containing the culture of the organism is placed in the water-bath and killed by heat and then carbolised.

Methods of Standardising the Vaccine.—Having prepared the vaccine it is necessary to estimate the dose of vaccine to be given. This can be done in one of several ways, and they may be briefly enumerated here, *i.e.*, by

(*a*) *Surface area of growth.*—It has been found in practice that on an evenly spread agar surface after 24 hours' incubation each square cm. will contain about 4000 million organism with fast growing organisms, and after 48 hours slow growing organisms, such as the pneumococci, stereptococci will only have multiplied to the extent that each square cm. of growth contains 2000 millions.

(*b*) *Counting an emulsion of the organism against an equal volume of blood.*

(*c*) *By opacity* (Brown's Method).—Comparing the opacity of the bacillary emulsion with a standard set of opacity tube. The tube that it matches corresponds to the opacity produced by the given number of the particular organism shown in the table supplied with the test set.

(*d*) *By drying the organism* after scraping the growth on the surface of the media and then weighing the bacterial mass. This is the method used for tuberculin, as the other methods are not applicable owing to the difficulty of breaking up the bacilli.

When the number and weight of organisms is known it can then be diluted down with 5 p.c. carbolic saline to the necessary dilution.

The test for toxicity should be done on animals with very toxic organisms, *e.g.* Shiga, pyocyaneus, etc. The test is very necessary as there are great variations in toxicity sometimes present.

Method of Injection of Vaccine.—When the dose is to be given, the neck of the glass ampoule, which has been previously well-shaken, is flamed and broken off with forceps sterilised in the flame, and the vaccine is drawn into the sterile syringe, the ampoule being held with the broken neck pointing downwards. The most convenient sites for subcutaneous injections are the upper arm near the insertion of the deltoid, or below the middle of the clavicle between it and the nipple. The skin over the spot selected for injection is disinfected with solution of iodine and the injection is given; a little iodine or collodion is finally applied to the puncture.

Control of Doses.—The dosage may be arrived at by considering the following factors:—

(*a*) *Toxicity of the Organism.*—The majority of the organisms we inject are highly toxic to man, *e.g.*, pneumococcus, gonococcus, streptococcus, B. pyocyaneus, coli, Shiga, etc., and an initial dose of 5 to 10 millions is ample. With organisms of low toxicity, *e.g.* B. typhosus, staphylococcus, etc., an initial dose of 100 to 500 million would not cause too violent general and local symptoms.

(*b*) *Stage of the Disease.*—In acute stages of the disease, ample toxins are already being formed and the dose should always be small; thus in typhoid, Malta fever, dysentery, glanders, etc., the initial dose should be about 1 to 5 million, and slowly increased. The same applies to open tuberculosis, when the T.B.E., should commence with 0.000000001. In subacute and chronic diseases much larger doses can be tolerated, *e.g.* 100 million.

(*c*) *Patient.—Age*, the dose can be regulated by the usual

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pharmacological rule of $\frac{\text{Age}}{\text{age}+12}$. *Race,* the Indian can usually stand larger doses of vaccines, other than tuberculin, which he is more sensitive to, than the European. *Colouration of the individual*, in practice one has noticed that light coloured individuals are more sensitive than the darker skinned.

(*d*) *Spacing and increasing the Dosage.*—Even when all these factors have been considered the first dose is purely an experimental one, and immunisation must be guided by watching the general, focal and local symptoms. The injections are given every three or four days until the maximum dose of 1 c.c. of 1000 million non-toxic organism, or 1 c.c. of 100 million of the more toxic ones. Three or four injections at weekly intervals are given when this dose has been reached. Usually one increases by multiples of the initial dose, *viz.*, 0.1 c.c., 0.2 c.c., 0.4 c.c., 0.8 c.c., 1 c.c. When injecting toxic organism and dealing with sensitive patients, or in acute conditions, the increases should be made more cautiously in half the arithmetical progression, *viz.*, 0.1 c.c., 0.15 c.c., 0.2 c.c., 0.3 c.c., 0.45 c.c., 0.75 c.c., 1 c.c. Both the increases and the proper spacing of the dosage must be judged by local and focal symptoms. Actual harm can be done by giving too big doses, whilst failure to respond may be due to employing too weak a dose. In cases that are doing well, the doses can be more rapidly increased without any harmful effects.

Immediate Effects of Vaccine

These may be local, general or focal.

(1) *Local reaction*, this is likely to appear after a prophylactic dose, *i.e.*, after a large dose. In curative treatment, when small doses are used, this reaction is as a rule not observed, unless the initial dose is large. It is doubtful if local reaction has any significance.

(2) *General reaction*, as a rule prophylactic use of vaccine is followed by this form of reaction. For instance, a rise of temperature, pains in the body or general aching, but these should subside within twelve to twenty-four hours. In the curative treatment, provided the dose is carefully regulated, general reaction that follows the prophylactic use is rarely seen. There may be a slight rise, say of one degree, and a general malaise. In fact the degree of general reaction is proportional to the amount used and the virulence of the bacterial endotoxin.

(3) *Focal reaction.*—An exacerbation of the inflammatory reaction, if present at the seat of the lesion, may take place. It should be looked upon as specific and requires careful watching. This reaction should not be aimed at, although a mild reaction is not necessarily prejudicial to the patient.

Varieties of Vaccines

Vaccines used may be of the following kinds :—

(*a*) *Ordinary vaccine.*—It is a simple suspension of killed bacteria in normal salt solution. The bacteria are killed either by heat, or autolysis, *i.e.*, allowing the organisms to undergo auto-digestion in an incubator after counting, or by some antiseptic, *e.g.*, cresol.

(*b*) *Sensitised or sero-vaccines.*—These are made by bringing bacterial emulsion in contact with appropriate immune serum. By this process the specific antibody in the serum becomes fixed by the bacteria and this combination is termed "sensitised" vaccine. It is doubtful however if any sensitisation takes place, or that the value of the vaccine is in any way enhanced.

(*c*) *Detoxiccated vaccines.*—These are vaccines with the endotoxin removed on the idea of introducing larger doses to get proportionately larger amount of antibody. Its practical usefulness in preference to ordinary vaccine has not been established although many prefer it.

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(*d*) *Immunogens.*—This is a more recent development and represents simple antigens almost free from toxins and from bacterial cells. In their preparation the organisms are grown on solid media, suspended in salt solution and then centrifugalised; the centrifugates forming the immunogens. Owing to their low protein content their use is not followed by any severe reactions and therefore can be given in larger doses. They may be used in acute and subacute conditions.

(*e*) *Formolised vaccines.*—It has been shown that when a toxin is treated with formalin it loses its toxic properties while retaining its antigenic power, *i.e.*, it ceases to be a toxin, although when injected into an animal it stimulates the production of antitoxin. These are known as "toxoids" in England and as "anatoxin" in France. They are used largely for immunisation against diphtheria (*see* page 639).

(*f*) *Diaplyte vaccines.*—Douglas and Fleming pointed out that when bacteria were extracted with acetone they did not lose their antigenic property, while some became easily dissolved in trypsin. It was subsequently shown that a tryptic digest of the acetone extracted bacteria acted as a good antigen. Dreyer "defatted" bacteria by first washing them in formalin and then extracting them with acetone. By this process the tubercle bacilli lose their acid-fast property and the streptococci and staphylococci become gram negative, at the same time they become soluble in trypsin. Tubercle diaplyte vaccine when injected into animals produce an anti-tuberculous serum which contains more antibodies than that produced by means of bacillary emulsion. Experience has shown that they have no special advantage over ordinary vaccines.

(*g*) *Antivirus.*—These are made by growing organisms for some weeks in broth until they cease to grow. Filtrates of such cultures contain a specific inhibitory substance which has been named by Besredka as "antivirus" (*see* page 634).

Prophylactic Vaccines

VACCINUM VACCINIAE, B.P.

Vaccine Lymph

It is a preparation of the substance obtained from the vesicle produced by inoculation of vaccinia virus on the skin of healthy animals, excluding bacterial contamination as far as possible. In viscid, colourless liquid, containing opaque white matter in suspension.

B.P. Dose.—0.06 mil or 1 minim (by scarification).

Action and Uses

The main object of vaccination is to confer immunity against small-pox. The protection is less perfect and less permanent than an attack of small-pox. The susceptibility to small-pox after primary vaccination returns slowly and the immunity wears off after six years, therefore re-vaccination should be done every seven years and oftener if exposed to infection. The immunity appears after one week, generally about the eighth day of successful vaccination. The vaccine virus grows and produces an enormous number of colonies at the inoculated spot by the 8th day, when the antibodies appear which attack and digest the colonies producing toxin which cause local redness and fever. Soon however the micro-organisms are killed and the contents of

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the pustules become inert, but antibodies remain for a long time in the body. At this period the subject remains hypersensitive, and if re-vaccinated may develop anaphylaxis.

As a rule no complication occurs if the operation is done under strict aseptic care. But cases of *post-vaccinal encephalitis* have been recorded occurring in adults previously unvaccinated. It appears 9 to 12 days after vaccination, the onset being abrupt and accompanied by headache, vomiting and drowsiness passing on to coma. It does not occur in primary vaccination of infants or in secondary vaccination. The cause of this complication is unknown. It may be due to vaccinia virus directly, or indirectly by the activation of some unknown latent virus.

Intraspinal, intramuscular or intravenous administration of serum from individuals who have recently been successfully vaccinated has been tried by the French physicians apparently with good results.

VACCINUM TYPHO-PARATYPHOSUM, B.P.

Anti-typhoid-paratyphoid Vaccine

Syn.—T.A.B. Vaccine.

It is a sterile suspension of the micro-organisms, *Bacillus typhosus*, *B. paratyphosus A*, and *B. paratyphosus B*, which have been killed. Contains 1000 million *B. typhosus*, 500 *million B. paratyphosus A*, and 500 million *B. paratyphosus B.* in 1 mil. In colourless opalescent liquid.

B.P. Dose.—First dose, **0.5 mil** followed after 7 to 10 days by the second dose of **1.0 mil** subcutaneously.

Action and Uses

T. A. B. vaccine is now largely used as a prophylactic against typhoid and paratyphoid infections, and is the routine method employed in the Army and in institutions where any case of typhoid occurs. The vaccine used in India for Army purposes contains 1000 millions *B. typhosus*, 750 millions *B. paratyphosus A* and 750 millions *B. paratyphosus B* per cubic centimetre. Two inoculations consisting of 0.5 c.c. and 1 c.c. are given at an interval of 7 to 10 days. There is generally some reaction after the first dose which consists of local tenderness and swelling with slight enlargement of the glands. A slight rise of temperature usually occurs with headache and general aching. The experience of the last war testifies to the high value of inoculation as a method of prophylaxis. In the Army in India this inoculation is repeated at intervals of 18 months. The duration of immunity is about 2 years or may be less.

The anti-typhoid vaccine (Wright) prepared from bouillon-grown cultures of *B. typhosus* only is not now used to any extent, suspensions from agar having replaced it. Vaccines consisting of *B. typhosus* without the addition of the paratyphoid strains are used in countries where the incidence of paratyphoid infections is low, e.g. U. S. A.

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Anti-plague vaccine.—The vaccine manufactured in India is that of Haffkine which consists of a bouillon culture of a virulent strain of *B. pestis* grown at 80°F. for four weeks, killed by heating at 55°C. and preserved by the addition of 0.5 per cent. phenol. The dose for adult males is 3 c.c. and for women 2 c.c. Proportionately smaller doses for children are given in relation to body weight. When freshly prepared, the vaccine may give a considerable degree of reaction and it is advised that, if used within three months of the date of manufacture, the standard dose be reduced to 2 c.c. Single dose inoculation is usually employed but, when practicable, the vaccine may be given in divided doses.

Anti-plague vaccines consisting of bacterial suspensions from agar cultures are prepared at the Lister Institute, London, and the Pasteur Institute, Paris, and elsewhere.

Anti-cholera vaccine.—The prophylactic anticholera vaccine contains 8000 millions killed vibrios per c.c.; 0.5 c.c. is given as the first dose and one c.c. as the 2nd dose. The local reaction is as a rule mild, but there may be œdema, and a painful infiltration at the site of the injection. Castellani recommended a mixed vaccine of *B. typhosus* and *B. paratyphosus A* and *B*, plus vibrio cholera, killed by 0.5 carbolic acid. The number of organisms per c.c. is as follows :—

Typhoid	...	1,000 millions
Paratyphoid A	...	750 ,,
Paratyphoid B	...	750 ,,
Cholera		10,000 ,,

About 8 ms. or 0.5 c.c. is given at the first injection and double the dose at the second a week later. It is an advantage to give a third inoculation (the same dose as the second) two weeks after the first. The reaction is not very severe and the inoculated persons are fit for work twenty-four to thirty-six hours after injection. The experience gained during the war was that the immunity obtained by these injections was of short duration.

Prophylactic vaccines have been used for the prevention of colds and pneumonia, and for dysentery in jails, asylums, etc.

Anti-rabic vaccine.—As the infecting agent in rabies cannot be cultivated on artificial media the vaccines used for anti-rabies prophylaxis are prepared from the brain and spinal cord of animals which contain the rabies virus. Pasteur found that when the virus from the dog was passaged through a series of rabbits by subdural inoculation it changed its character and became 'fixed.' This 'fixed virus' is considered not to be infective for man by inoculation into the skin or subcutaneous tissues. All anti-rabic vaccines are prepared from fixed virus and several methods of preparation are employed. Pasteur's original method, which is still in use in Paris and in other Pasteur Institutes, consisted in giving a series of doses of emulsions of spinal cord of passage rabbits subjected to dessication for different periods. Live fixed virus is present in the Pasteur vaccine. The method in use in India, introduced by Semple, is the preparation of an emulsion of the brain and spinal cord of passage rabbits treated with 1 per cent. carbolic acid at 37°C. for 24 hours and subsequently diluted to reduce the carbolic acid to 0.5 per cent. Semple's original treatment consisted of the daily inculation of 5 c.c. of a 1 per cent. emulsion for 14 days. The dosage now employed is adjusted to the estimated severity of the bite, courses of treatment varying from 7 to 21 days being given and the strength of the vaccine varying from 2 per cent. to 5 per cent. passage brain. Sheep's brain is now used for bulk production of the vaccine. As the carbolised anti-rabic vaccine does not contain living virus and retains its prophylactic value for over 6 months it is not necessary for patients to be treated at a Pasteur Institute. The vaccine can be sent out to hospitals and dispensaries where treatment is easily accessible to patients. Numerous such centres have been established in India. Neuroparalytic

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accidents have sometimes followed the use of anti-rabic vaccine but these are very rare with the carbolised vaccine and are seldom fatal.

Curative Vaccines

After the discovery of the antitoxin for diphtheria there was a rush to manufacture serums for every known bacterial disease. A few years' trial convinced the majority of medical men of the uselessness of many of these antisera, with the result that majority have disappeared in the routine treatment of disease. So it was with vaccine therapy, after the discovery by Wright of antityphoid inoculations, and the value of staphylococcus vaccines for the cure of boils, etc., a boom was started in vaccine therapy, and all and sundry were inoculated with a vaccine made from an organism that was supposed to have caused the disease. Out of this class, the following is a sane view of this very useful therapeutic agent.

(*a*) *The Limitation of Vaccine Therapy.*—Immunity takes time to develop, 2 to 3 weeks; vaccines are therefore useless in acute diseases like pneumonia, and should be reserved for subacute and chronic affections. The blood fluids containing the antibodies must have access to the causative organism, therefore they are useless in typhoid infections of the gall bladder, and restricted in use for tuberculosis owing to the endarteritis present. The difficulty of keeping the secondary infections under control in infections of the lung, bowel, etc., and the tendency for the bacteriologist to forget the value of treatment other than vaccines.

(*b*) *The uses of vaccine therapy* are therefore reserved for subacute or chronic diseases; when the infective organism can readily be obtained in pure cultures; and when the antibodies produced by the graduated inoculation of these dead bacillary emulsions can come in intimate contact with the organisms producing the disease; and the secondary infective flora can be limited by proper treatment.

The most important of these vaccines are :—

Wright's Staphylococcal Vaccines.—The vaccine is prepared from the organisms found in the pus. The initial dose is 100 millions increased up to 1000 to 2000 millions. The vaccine has proved most useful in furunculosis, folliculitis of the beard (sycosis), axilla and buttocks, in the secondary infections in acne. In sinuses where no dead bone, etc., is present, and to diminish the scar tissue after synovitis of the tendon sheaths.

Streptococcal Vaccines.—The initial dose is 5 millions increased gradually to 100 millions. The difficulty in preparing the vaccine lies (i) in getting the organism to grow on media, (ii) it is rarely found in pure cultures, and (iii) the identification of the pathogenic strains. Its greatest use is in eczematous conditions of the skin combined with stapylococcus vaccine. It has a limited use in chronic rheumatoid arthritis, and sprue conditions of the gut.

B. pyocyaneus.—Dose, 10 to 100 millions, useful in ulcerations of the skin, and in surgical sinuses.

B. coli.—Dose, 10 millions up to 100 millions, depending on the toxicity of the strain. The initial dose should be less, 2½ millions. Of great value in *infection of the bladder* and *septic cystitis* and *pyeliltis* of pregnant women. Sometimes of use in *mucous colitis.* Also useful in *puerperal sepsis* when urine culture shows growth of *B. coli.*

B. dysenteriæ.—*Shiga's bacillus.*—Dose, 10 to 100 millions; Flexner's, 100 to 1000 millions. Very useful in the chronic bacillary dysenteries seen in the tropics resembling a sprue. In these infections the intestinal ulcers have frequently streptococcus as a secondary infection.

D. gonococcus.—Dose, 10 to 100 millions, and should be recently made, otherwise the toxin rapidly deteriorates. The majority of cases that come for treatment are old standing cases of gleet, where

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a secondary infection has been superadded by uretheral injections or instruments. It is not useful in acute cases, but in secondary symptoms of gonococcal infections, *e.g.*, *arthritis*, *orchitis*, *pelvic inflammations*, etc., it gives much relief.

Pertussis Vaccine. *Syn.—Whooping Cough Vaccine.*—A sterile suspension of *Bacillus pertussis* (*Hæmophilus pertussis*) made from freshly isolated cultures or from cultures preserved in such a way as to retain their antigenic powers. The administration of this vaccine is indicated in the prevention and treatment of **whooping cough.** Inoculation of contacts confers some immunity against an attack and is therefore useful in controlling the spread of the disease. Since other organisms are found as secondary invadors, a mixed vaccine consisting of pneumococcus, B. influenzæ, M. catarrhalis, staphylococcus aureus and streptococcus hæmolyticus and non-hæmolyticus is often used. Sometimes it is mixed with only B. influenzæ and pneumococcus.

Dose.—Prophylactic, 800 million, 1600 million and 3200 million organisms at intervals of three to four days. *Curative*, intial dose 250 million, gradually increased.

Pneumococcus Vaccine.—Pneumococcus exhibits three serological groups—types I,II and III; and a heterogeneous group, comprising all those which do not conform to any of the other three types, is termed type IV.

This vaccine is used in chronic and subacute infections with pneumococcus, such as empyema, arthritis, etc. It is also useful in acute lobar pneumonia and broncho-pneumonia, and when given to susceptible individuals who were exposed to infection it will abort the attack.

Dose.—25 to 50 million organisms in chronic cases, to be followed at intervals of 5 to 7 days, by further injections up to the maximum of 2000 million, the aim being to build up rapid immunity without causing any focal reaction. In *acute lobar pneumonia*, the initial dose should not be more than 5 million, this may be doubled after 24 hours.

In chronic bronchitis and asthma, numerous organisms have been used in the treatment of these conditions sometimes with great benefit. The difficulty lies in finding the causative bacillus and preventing secondary infections. The following organisms have been used: *B. influenzæ*, dose 10 to 100 millions; *M. catarrhalis*, 100 to 1000 millions; *B. septus*, 100 to 1000 millions; *Streptococcus hæmolyticus*, 10 to 100 millions.

TUBERCULINUM PRISTINUM, B.P.

Old Tuberculin

It is the concentrated filtrate from a fluid medium on which *Bacillus Tuberculosis* has been grown. Supplied in transparent, viscous fluid, yellow to brown colour, odour like honey.

B.P. Dose.—(For diagnosis) **0.001 to 0.005 mil.** or $^1/_{60}$ **to** $^1/_{12}$ **minim** by subcutaneous injection. (Therapeutic) **0.000001 mil** gradually increased; or $^1/_{600000}$ **minim** gradually increased, by subcutaneous injection.

Action and Uses

The chief use of old tuberculin is for diagnostic purposes known as von Pirquet test. The required amount is placed on the skin and introduced by scarification. In tuberculosis there is swelling with a red flush after 24 hours. It may also be used diluted, subcutaneously into the skin and the presence of tuberculosis is indicated by local induration and redness. A febrile reaction to any dose of old tuberculin up to 0.001 c.c.

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means definite activity, no reaction to 0.01 excludes active disease. Reactions to about 0.005 are indefinite. The tuberculous patient may react either locally at the site of the injection, focally with exacerbation of signs in the lesion, or generally by a rise of temperature. It is the rise of temperature only which is used in the subcutaneous test. * This test is more valuable in children than adults.

The tubercle bacillus is said to consist of: (*a*) a protein part which only can make the uninfected body allergic, and produce a reaction in the allergic body; (*b*) a lipin part, which causes cell necrosis; and (*c*) a carbohydrate part. *Purified protein derivative* obtained from standard tuberculin (Tuberculin P.P.D.) is now available and is used for testing by the intradermal method, the dose being 0.00002 mg., and failing a reaction, 0·005 mg. is then given. Positive reactions may be classified as follows :—

\+ swelling from 5-10 mm. in diameter.
\+ + swelling from 10-20 mm.
\+ + + swelling more than 20 mm.
\+ + + + swelling and necrosis. †

For curative purposes the injections are given in very minute doses, and gradually increased according to the reactions, as evidenced by rise of temperature, and other local and general reactions. But this vaccine proved a failure owing to excessive toxicity, and Koch ground up the bacilli in saline solution and allowed the emulsion to stand for some hours. The upper layer, *Tuberculin ober*—T.O. he found contained the fever producing element; the deposit—*Tuberculin ruckstand*—T.R. was comparatively free from this danger. This residue was well washed and made up in 20 p.c. glycerin, the present day T. R. on the market. Wright showed that the German school had been using too large doses, which was the reason of their failure. He used the tubercle bacillus dried and ground up in an emulsion with saline—*Tuberculin Bacillary Emulsion*—T.B.E. and there are two varieties on the market, *bovine* and *human T.B.E.* As it is almost impossible to count the bacilli owing to morphological variations, the dose is estimated in milligrams of dried bacillary substance.

The following may be taken as representing the present trend of opinion on the value of Tuberculin :—

(1) *Tuberculin* (T.B.E.) should be given in very small doses, 0.000000001 mgrm. and gradually raised, and should not exceed 0.001 mgrm.

(2) The dose should be controlled by general reactions, fever, pulse; local reactions at the site of inoculation; and focal reactions at the site of the disease. The dosage should not be increased if these reactions are excessive.

* Halliday Sutherland, *Medical Press and Circular, 1934*
† Long, Seibert and Aronson, *Tubercle,* 1935

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(3) The treatment is most useful in surgical tuberculosis of joints and glands due more often to the bovine type; of limited value in chronic tuberculosis of the lungs and intestines.

(4) Tuberculin should not be employed in the acute stage of the disease.

Recently much attention is being paid to the prevention of tuberculosis, and the main principles in this direction are (1) destruction of the infection, and (2) increase of individual resistance. With this object in view the following methods have been advocated to obtain immunity, *viz.*—

(*a*) *Injection of living virulent tubercle bacilli.* This was found to be too dangerous to try on human beings.

(*b*) *Use of avirulent tubercle bacilli.* The latest attempt to attain this object is by the injection of **B.C.G.Vaccine** (Bacillus Calmette-Guerin). This consists of bovine tubercle bacillus attenuated by 230 passages in 13 years on potato-glycerin and bile. Inspite of varying experimental reports B.C.G. vaccine injected subcutaneously give relative immunity for a time, but how long this lasts is not known.

It may be given by the mouth but the results have not been very successful. Subcutaneous injections sometimes give rise to cold abscess, but less when the dose is 0.03 to 0.02 mgrm. The effect of B.C.G. vaccine as summarised by Heimbeck is that it tends to produce a moderate immunity before the appearance of allergy manifested by positive Pirquet reaction. It is not strong enough to prevent infection, but prevents the infection from becoming malignant and renders it benign, so that it acts like a new dose of vaccine increasing the antibody to a point where it gives an allergic reaction.

The Causes of Failure of Vaccine Therapy

The commonest cause is due to the fact that the wrong organism is isolated. To avoid this, two to three cultures on different media should be taken. If the benefit produced does not go on to cure, another culture should be made, *e.g.* in an acute eczema, at first only the staphylococcus aureus and albus can be isolated, when the acute symptoms subside and the eczema weeps serum, streptococcus may then be recovered from the serum. The dose may be too small, or too large. An individual factor may also be present, thus an adult with plenty of bone and muscle usually gives a good response, whilst the old and feeble are bad subjects for immunisation. Rarely one meets with individuals who are hypersensitive to these injections, for them the dose has to be very carefully and gradually increased, otherwise more harm than good will be done.

The Abuses of Vaccine Therapy

From what has already been said, vaccines should not be employed

(1) *In acute diseases, viz.* pneumonia, septicæmia, erysipelas, and acute tuberculosis.

(2) *When dead tissue, viz. necrosis or abscesses are present.* These conditions should be treated surgically, and repair hastened by the

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proper application of vaccines. Nobody would try to save a gangrenous leg by vaccine therapy, yet one has seen large psoas abscess, softened glands in the neck, sinuses with necrosed bone, given vaccines.

(3) *When the causative organism has not been diagnosed, e.g.* the use of coli vaccines in an unknown fever, the blunderbuss vaccines employed for the treatment of chronic bronchitis, injecting non-pathogenic streptococci in rheumatoid arthritis.

(4) *When the organisms are not in contact with the antibodies present in the blood, e.g.* in superficial infections of the throat and nasal mucous membranes, the use of the acne bacillus in preventing comedones, etc.

Protein Therapy

Within recent years much doubt has been thrown on the specificity of the vaccines and sera used in the treatment of different diseases, since it has been found that a non-specific vaccine may sometimes be not only useful, but even act better than a specific vaccine in the treatment of a particular disease. Thus, it has been shown that some forms of gonococcus infections are greatly benefited by injections of other vaccines, *e.g.* typhoid vaccine. Upon this is based non-specific protein therapy. It appears that the good effects observed by giving injections of peptone solutions, milk, etc., are due not so much to the presence of any specific substance, but possibly to the special kinds of foreign proteins which these injections may contain. Similarly normal horse-serum, sodium nucleinate, bacterial proteins and non-proteins like colloidal metals have been injected to provoke a reaction of the body's defensive mechanism. The popular method of utilising protein therapy is by the injection of sterile milk, and the beneficial effects are due to the production of vaso-dilatation and consequent flooding of the diseased tissues with antibodies. Preparations available for the purpose are:—**Lactumin, Lactolan** and **Aolan.**

Protein injections may be used therapeutically for the following purpose:—

1. *Desensitisation.*—It has been observed that certain individuals develop asthma, hay fever, urticaria, angioneurotic œdema, etc., due to their sensitiveness or idiosyncrasies to certain proteins. Whether it is the actual food that causes the above conditions, or whether the particular foodstuff which produces within the system an antifood protein body to which he is too sensitive, is however uncertain.

This sensitiveness to special proteins can be tested by different food products. The method followed is like doing multiple Von Pirquet's reactions, using the dried extracts in place of the tuberculin. It is generally done by scratching in regular sequence upon some surface of the body, generally the forearm, and into each successively is rubbed the product to which it is desired to test the sensitiveness of the patient. If the patient gives a strong reaction at one of the inoculated spots, it is regarded as evidence of his sensitiveness to this special substance.

Once the case is established the patient is treated either by avoiding the particular food substance or by producing desensitisation by injecting either a specific protein (antigen) to which he is sensitive, or by a non-specific protein like peptone or milk. The initial dose should be very small to avoid any reaction. Subsequent injections are given weekly, increasing the dose with each injection.

2. Non-specific protein when injected parenterally is followed within a short time (generally from a few minutes to one hour) by a rise of temperature, chill, sweating and leukopenia followed by leucocytosis. These reactions are more evident after intravenous injection, and after intramuscular injection in susceptible persons.

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Coincidently with these changes there is an increase in the antibodies and an improvement in the general condition of the patient, and a subsidence of the pain and other symptoms. The improvement is often temporary, but some patients show permanent improvement.

Protein therapy has been found efficacious in **acute** and **sub-acute arthritis, gastric** and **duodenal ulcers.** Acute **iritis** and other diseases of the eye due to local infection improve with parenteral injection of milk. The usual dose is 5 c.c. boiled for 4 minutes, or any of the preparations available for the purpose may be used. Similarly intragluteal injections have been used in subacute and chronic **gonorrhœal arthritis,** sometimes with good results. **Urticaria, migraine** and attacks of **asthma** being due to hypersensitiveness to certain proteins, oral use of peptone is a simple and harmless method of checking these attacks. Injections of **Yatren-Casein, Lactolan,** or **Aolan** (sterile and toxin-free milk albumin) have yielded good results in gynæcological practice attended with chronic inflammation of the appendages.

Contra-indications.--Uncompensated cardiac lesion, acute endocarditis and pericarditis.

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PART V

RADIATION THERAPY

ULTRA-VIOLET RAYS

Light is caused by the periodic vibration or rotation of electrons, and is the result of waves of energy transmitted through the ether. The visible light rays of the sun are composed of seven primary colours, at one end of which are the red rays and at the other the blue and the violet. In addition to these there are invisible light rays. At one end of the visible spectrum are invisible rays known as the *infra-red rays* and at the other the *ultra-violet rays*. The ultra-violet rays are the chemical rays, so called from the chemical changes they produce when projected on a sensitive medium. They are invisible light vibrations, between 400 to 100 millimicrons in length. The infra-red rays include the dark heat rays.

The composition of the rays of the sun varies with the altitude and the purity of the atmosphere. In fact the atmosphere screens off the harmful radiations. The ultra-violet rays are easily destroyed or made ineffective by moisture, dust and organic matters present in the atmosphere. In pure air there are more ultra-violet rays, so that the more purified air of mountain may contain twice as much ultra-violet rays as that of the air of the plain.

The biological action of sunlight depends upon its intensity and power of penetration and absorption. An excess of heat rays is harmful, and it is to the preponderance of heat rays that the harmful effects of the tropical sun are due. Sunlight, as is well known, is essential to the well-being of all living beings, both animal and vegetable. But it is to the ultra-violet rays that most of the therapeutic effects of solar radiation are attributed.

The first effect of exposure is vaso-dilatation and œdema of the soft tissue, this acts as a counter-irritant and relieves congestion of the internal organs. After a latent period of four to eight hours there is erythema of the skin, although the patient may not feel anything at the time of exposure. The next effect is sterilisation of the superficial tissues. The short rays are strongly bactericidal, and these are filtered out by impurities in the atmosphere before the long rays. The rays of the sun have much more bactericidal effect at high altitude than at low ones. After a few exposures there is pigmentation of the skin which is much the same as that produced from exposure to sun's rays. This pigment protects the body against the ultra-violet rays, and after this is formed one can stand larger doses of the rays. The response of the skin to light varies, some skins being highly sensitive.

There is evidence that exposure of an infected area inhibits the growth of micro-organisms, probably by forming some germ-killing body in the infected tissue. The other important effect is the **regulation of calcium metabolism** (*see* page 95). Gates and Grant have shown that in partially parathyroidectomised animals irradiation had a definite influence in preventing tetany, and that there was a rise of serum calcium after a steep decline. It bears a definite relation to body metabolism associated with parathyroid physiology, and in the absence of factors which light represents, an attempt to compensate is made by over-activity of the parathyroids.

A powerful ray alters the proteins of the skin, and these abnormal proteins when absorbed, give rise to allergic condition in the skin making it intolerant to light. The ergosterol of the skin is activated by these rays and acquires an *antirachitic property*.

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Immense possibilities of treatment by Heliotherapy has been proved by Rollier, who exposed his patients to sun's rays in the Alps. Indeed the ideal treatment for lupus, surgical tuberculosis and rickets is by Heliotherapy at a higher altitude, where a much greater intensity of direct sunlight can be borne. But owing to the climatic and other conditions that prevail it is not possible to practise direct sunlight treatment, except on a limited scale or in certain selected parts in India. Therefore the treatment by ultra-violet rays is done chiefly by artificial light, and electric incandescent and arc lights are largely used for the purpose. Electric lights possess properties similar to those of sunlight. The arc light is full of luminous rays but there is also a good proportion of the rays at the violet end of the spectrum and a fair amount of the ultra-violet rays. In the incandescent lamp the heat rays predominate, the ultra-violet rays are absent, being removed by the glass globe. Arons in 1892 was able to electrify mercury vapour and produce a light devoid of orange and red rays. Subsequently Cooper-Hewitt perfected this in a glass vacuum tube, so that when quartz is substituted for glass, the small amount of ultra-violet radiation given off by the incandescent lamp can be made available. The mercury vapour lamp, which is known as the "Kromayer lamp" is therefore largely used. This consists of a tube from which air has been exhausted and which is filled with mercury and mercury vapour.

The advantages of carbon arc lamp are, (*a*) the output of ultra-violet rays being small the chances of an overdosage are less and no harmful effects are observed; (*b*) for the same reason can be used for treating weak and debilitated patients in whom the use of mercury vapour lamp may be harmful; and (*c*) a large number of patients can be treated at the same time, since slight errors of timing are not attended with any signs of overdosage.

The disadvantages are :—(*a*) consume a large amount of current and give off CO_2; (*b*) the electrode may burn unequally in open arc pattern; and (*c*) the output of ultra-violet rays being less the results are slow.

The ultra-violet rays only penetrate a short distance, the hæmoglobin of the blood acting as a red filter screen. Under compression from surface quartz applicators or other means, the depth of penetration is increased. It is important to note that these actinic rays do not pass through glass, paper, thin cloth or ointment, but will pass through sterile water. *Vita glass* permits wave lengths up to 2000 Angstrom units to pass through it.

The therapeutic applications of ultra-violet rays are many. Their power to cure **surgical tuberculosis** and **rickets**, to accelerate the healing of wounds and to improve the general health of weakly children has been well established. Many chronic skin diseases rebellious to other forms of treatment often yield good results when exposed to these rays, using the tungsten arc lamp. **Lupus, rodent ulcer** and **X-ray dermatitis** are successfully treated with these rays. **Septic wounds, sinuses,** and **chronic ulcers** heal quickly. Good results have been reported in the treatment of chronic **articular rheumatism, myalgia, fibrositis** and **rheumatoid arthritis.** In many depressed states of the health and **neurasthenia,** a brief exposure often gives a feeling of stimulation and a sense of well-being.

Method of administration.—This varies with the type of lamp used, the depth and extent of lesion, the power of resistance, the idiosyncrasy, and the sex of the patient. An average distance of three feet with mercury vapour lamp, and of 18-in. or less with arc lamp is considered as the average standard. The starting dose should not be more than one minute for mercury, and two minutes for carbon arc lamp. The following points require careful consideration in all cases :—

1. The eyes of both the patient and the operator must be protected

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by suitable goggles. Ordinary tainted or smoked glass does not offer sufficient protection.

2. For other parts of the body not intended for exposure, ordinary clothing affords sufficient protection.

3. Children can stand relatively larger doses; women are more sensitive than men.

4. The exposure should be given once, twice or three times a week according to the condition of the trouble.

5. After continuous exposure for three months for half an hour at a time there should be a pause for several weeks.

Contra-indications.—The application is harmful to highly nervous and neurotic people and in various forms of neuritis, where it may do definite and irretrievable harm. The following conditions either contra-indicate or require modification of the dosage ordinarily given :—

1. Extremely sensitive skin.
2. Arterio-sclerosis or advanced valvular diseases of the heart.
3. Active pulmonary tuberculosis with fever. A focus of early and latent phthisis may flare up into activity through injudicious use.
4. Acute illness.
5. A tendency to hæmorrhage. It should not be given in hæmoptysis or in those suffering from hæmophilia.
6. Chronic nephritis or quiescent appendicitis.

Untoward effects.—The belief that ultra-violet radiation is beneficial in almost any condition and that it does no harm is a mistake. While it does good in some conditions it is injurious and positively harmful in others. A common effect of overdosing apart from that of the skin, is sleeplessness, restlessness, lassitude, loss of weight and nausea. Exposure of an extensive surface lessens resistance to bacterial infection. Eczema and many forms of skin affections are aggravated by these rays, while senile cataract has been known to follow its use when proper protection has not been taken for the eyes. A case of severe burn followed by duodenal ulcer has been recorded.

RADIUM

Radium is an element of the strontium-barium group and forms four important salts, *viz.* bromide, chloride, carbonate and sulphate. It is constantly undergoing transformations into other substances, and becomes successively emanations of radium A, B, C, D, E, F. During these changes energy is radiated from the substance in the form of so-called *Alpha, Beta* and *Gamma* rays, upon the various effects of which its therapeutic action depends. Radium emanation is a gas which is scattered in the air. It is therefore put in sealed containers where emanation gradually accumulates until a maximum is reached when it is converted successively into different forms of the series. A sealed preparation of radium element or emanation emits the three types of rays, each of which has the following characters :—

The α rays travel at the rate of 18,000 miles a second, but they have very little penetrating power. As they cannot pass through a thin sheet of paper, glass, or the metal wall of the emanation containers, they have very little therapeutic value, except in the treatment of superficial lesions of the skin.

The β rays travel at the rate of 60 to 180,000 miles a second and penetrate about 8 mm. of tissue, but cannot penetrate over 2 mm. of lead or 1.2 mm. of brass.

The γ rays are vibrations of ether and are analogous to X-rays or ordinary light. These have greater penetrating power.

Therapeutically *Beta* and *Gamma* rays may be used either together, or singly, the other rays being excluded by suitable screening. Certain substances (lead, silver, platinum, etc.) offer resistance to the passage of the different radium rays and these are used as screens.

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β radiation is used chiefly in the treatment of diseases of the skin and affections of the mucous membranes, and the exposure is so regulated as to produce only definite surface radium reaction (Superficial Radium Therapy). Its action is much the same as cautery, diathermy or carbon dioxide snow.

Beta and *Gamma rays* are employed when dealing with malignant disease and morbid conditions of the pharynx and larynx, and other deep seated organs, *e.g.* the stomach, intestine, uterus, etc. (Deep Radium Therapy).

Action and Uses

Some believe radium to be the most expensive and efficient form of cautery as yet discovered, while others maintain that it has a marked selective action in destroying pathological tissues without affecting normal tissue. The effect varies with different growths and even in normal tissues.

Radium emanation if of sufficient intensity and acts for sufficient length of time has three distinct effects on the living cells, *viz.*— (1) Increase of cell activity with possible associated proliferation; (2) arrest of cell activity; and (3) degeneration and destruction of cell. The effects are not apparent immediately after exposure. Generally 1 to 2 days or even 2 to 3 weeks pass before any change is observed. This latent period varies with the strength of the source of energy and the amount of filtration and protection used.

Because of its destructive effect on certain forms of tumour cells, the chief application of radium is found in surgery. Although it cannot replace surgery, some permanent cures of superficial cancer of the skin of the basal-celled type have been recorded when properly treated. Rapidly growing cellular types of malignant disease often show at least a temporary set-back. As a palliative in subduing hæmorrhage, relieving pain, arresting discharge and offending odour and in prolonging life at least temporarily, its value is undisputed.

It has been successfully used in **rodent ulcers, epitheliomata** of the skin and **keloids**, while some cases of successful treatment of tumours of the brain are also recorded. In **lymphomas** and **Hodgkin's disease**, application of radium reduces the size of the involved glands, but whether any permanent cure is effected is doubtful. Similarly improvement has been noticed in both **simple** and **exophthalmic goitre.**

Its use in the treatment of cancer of the **rectum** is followed by good results, but do not justify its use as a substitute for operation. The best results are obtained in **epithelioma** of the **anus** and in the low growths of the posterior wall. Its use in the **carcinoma** of the **breast** has been followed by remarkable results and it is now recognised that early cases can be treated as successfully by radium as by operation. In the treatment of **carcinoma** of the **cervix uteri**, "split doses" or repeated treatment at brief intervals as recommended by Heymann of Stockholm is generally followed. In borderline and inoperable cases, radium is the method of choice and gives better results than X-rays. In **fibroma** and **fibromyomata** of the uterus, its use has been attended with encouraging results.

Method of Application

The main principle underlying all radium therapy is the correct estimation of dosage and exposure necessary to bring about the death of pathological cell without markedly affecting the function and vitality of the normal ones. An insufficient dose may act as a stimulus and thus aggravate the condition; while an over-dose may destroy normal tissue. The source of radiation should be standardised under the exact conditions in which it is to be employed. The duration, the amount of radio-active element, filtration, distance, and

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susceptibility of the skin and the general vitality of the patient demand careful consideration. The intensity and quality of the rays depend on the amount of radio-active substance, the distance from the patient and the filtration used, while the effects depend on the rays absorbed by the tissue. The dose for surgical use is usually from 50 to 200 mgrms. For superficial skin lesions smaller doses are used, while for large deep-seated growths larger doses are necessary.

Methods of administration.—For therapeutic purposes radium may be applied in the following ways :—

1. *In platinum tubes or needles.*—This prevents the alpha and beta rays. Each tube contains 2 to 3 mgrm. of radium with 0.5 to 0.8 mm. of platinum screening. This gives quite good results.

2. *Radon seeds.*—Radium emanation or radon is a gas soluble in water, which can be stored in small tubes or seeds. These seeds are minute needles of gold or platinum which contain minute glass tubes of radium emanation. These seeds are inserted in diseased tissues with special form of canula and left permanently there. They are therefore of special use in the treatment of diseases of the abdominal cavity where one can be inserted and left inside, thus avoiding another operation. They cease to give off rays after ten days.

Acute constitutional symptoms follow surface and distance therapy with large quantity of radium, than with interstitial radiation. Malaise, headache, nausea, and diarrhœa are generally observed. Irradiation of the upper abdomen is often followed by more severe constitutional disturbance than of head, neck, or pelvis.

Local changes in those handling radium are chiefly due to *alpha* and *beta* rays, and produce blunting of sensation of the finger tips, paræsthesia and anæsthesia, thickness of the epidermis and chronic dermatitis. If injury is severe, healing rarely occurs; hair follicles, sebaceous and sweat glands disappear. Telangiectasis and pigmentary changes with chronic ulcerations may also take place.

The *constitutional disturbances* have been attributed to cellular destruction and consequent protein absorption, Patients already in toxic condition are more susceptible to radium sickness. The mechanism by which tissue destruction provokes these symptoms is not fully understood. They may be a form of anaphylaxis or may be due to diverse metabolic changes at different stages of irradiation.

The following points should be noted in the therapeutic use of radium, *viz.*,

(1) That its intensity varies with the length of exposure. A short exposure causes stimulation of the tissues, a longer exposure inflammation, and a prolonged exposure destruction of the cells.

(2) That healthy cells react to radiation in proportion to their rate of growth. Lymphatic organs, hair follicles, glands of the skin, testicles and ovaries are particularly sensitive and are easily destroyed; while cartilage, bone, muscle, connective and nerve tissues are resistant to radiation. Diseased cells are more readily destroyed than healthy ones.

(3) That malignant cells and the cells of a more rapidly growing tumour are more easily affected by radiation than normal ones.

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PART VI

INDIAN INDIGENOUS DRUGS

N.B.—In this section only some important and commonly used drugs will be discussed. For a more exhaustive information the reader is referred to Col. R. N. Chopra's "Indigenous Drugs of India."

Expectorants and Bronchial Antispasmodics

ADHATODA

Syn.—*Bakasa*, Beng. *Arusha*, Hind.

Source.—The fresh and the dried leaves of *Adhatoda Vasica (Justicia adhatoda)*.

Composition.—(1) *Vasicine*, a crystalline alkaloid. (2) An *organic acid* (adhatodic acid). (3) *Ammonia*.

Preparations

1. **Tinctura Adhatodæ.**—Dried powder 2½ ozs., Alcohol (60 p.c.) *q.s.* to produce 1 pint by percolation. *Dose.*—½ to 1 dr or 2 to 4 mils.
2. **Syrupus Adhatodæ.**—Can be prepared by adding 1 of liquid extract to syrup 8. *Dose.*—1 to 2 drs. or 4 to 8 mils.

Pharmacology and Therapeutics

Externally.—The leaves possess **insecticide** properties, and are therefore considered to be a valuable remedy for blight on tea and other crops.

Internally.—Both the leaves and roots are stimulant **expectorants** and **bronchial antispasmodics.** The root may be used as a substitute for senega. It is an excellent remedy for **chronic bronchitis, phthisis** and **bronchial asthma.** It acts by virtue of vasicine which relaxes the bronchial muscles by depressing the vagus endings (Chopra and S. Ghosh). The decoction of the root bark is frequently used by the people of this country in catarrh, mild fever and bronchitis. It is useful in mild forms of **pertussis,** especially when complicated with bronchitis. The leaves smoked in the form of cigarettes relieve **asthma,** as they evolve ammoniacal vapour when burnt. It forms a vehicle for cough mixtures and is largely used in the form of Syrupus Vasaka et Tolu with Hypophosphites.

SAUSSUREA LAPPA

Syn.—The Costus. Kut.

Source.—The dried root of *Saussurea lappa,* with pungent aromatic odour and a pungent taste.

Composition.—(1) *Saussurine*, an alkaloid. (2) An aromatic oil. (3) Resin, tannin, bitter substances, inulin, etc.

Action and Uses

Kut has been used in India as a **tonic, antiperiodic** and **aphrodisiac.** The essential oil is an antiseptic and is eliminated by the genito-urinary tract which it stimulates. It is possible that the aphrodisiac effect is due to local irritation. Saussurine causes **relaxation** of the **bronchial muscles** partly by direct action on the muscle, and partly through the vagus (Chopra). The essential oil acts as an expectorant while excreted through the bronchial mucous membrane. It is there-

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fore largely used in the treatment of **bronchial asthma**, and as an **expectorant** in the form of the liquid extract (½ to 1 dr.) either alone or with other expectorants like potassium iodide. It is also used as a **carminative** and **diuretic.**

Laxatives

BELAE FRUCTUS

Source.—The fresh half-ripe fruit of *Ægle Marmelos.*

Composition.—(1) *Marmelosin*, the important active principle. (2) Tannin. (3) *Pectin. Mucilaginous principles*, sugar, etc.

Preparations

1. **Extractum Belæ Liquidum.**—1 in 1. *Dose.*—1 to 2 drs. or 4 to 8 mils.
2. **Decoctum Belæ, B.P.C.**—Bael fruit small pieces 8 oz., boiling water *q.s.* 20 oz. *Dose.*—½ to 2 oz. or 15 to 60 mils.

Pharmacology and Therapeutics

Internally.—The pulp of the ripe fruit is a **laxative**, and is valuable in **spastic** and **chronic constipation.** The pulp may be taken itself or may be made into a sherbet by soaking in water and then straining it. A little sugar may be added if required. The unripe pulp roasted, or a decoction made from the unripe slices dried in the sun (*Bael suti*) is astringent and is therefore used in **mucous diarrhœa** and **dysentery.** As a demulcent and mild laxative the ripe fruit may be used during convalscence from **dysentery** and early stage of **sprue.** The compound or dietetic bael powder (powdered pulp 1, arrowroot 1) may be used in the same class of cases. The ripe pulp is very serviceable in obstinate **catarrhal diarrhœa, chronic dysentery** and certain forms of **dyspepsia** characterised by alternate constipation and diarrhœa.

The root-bark of the plant is a mild febrifuge and enters into the composition of the "ten roots"—*dasha mula*—so frequently prescribed in mild fevers by the *Kavirajes.*

Drastic Purgatives

TURPETHUM

Syn.—*Teuri*, Beng. *Tarbad*, Hind.

Source.—The dried root and stem of *Ipomœa Turpethum.*

Composition.—(1) A resin, *Turpethin.* The root contains 5 to 10 p.c. (2) A fatty substance. (3) A volatile oil. (4) Albumin, starch, yellow colouring matter, lignin, salts and ferric oxide.

Dose.—5 to 20 grs. or 0.3 to 1.2 G.

Preparation

1. **Tinctura Jalapæ Composita.**—Jalap 80 G., scammony resin 15 G., turpeth 10 G., alcohol (60 p.c.) *q.s.* to 1000 mils. *Dose.*—½ to 1 dr. or 2 to 4 mils.

Pharmacology and Therapeutics

As a **purgative** it is *equal to jalap* and *superior to rhubarb*; it has moreover a great advantage over both these drugs in that it is free from nauseous smell and taste. It also acts very efficiently when given alone. It is often necessary to give it in larger doses than jalap, but this is no disadvantage. It has been in use in India as a **cathartic** from a very early date. When combined with chebulic myrobalans, it is useful in **dropsy.** The usual method of administra-

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tion is to rub down about a drachm of the root or stem with water and add to it some rock-salt and ginger, or sugar and black pepper.

KALADANA

Syn.—Pharbitis Seeds.

Source.—The dried seeds of *Ipomœa hederacea*.

Composition.—*Pharbitisin*, a resin, about 8 p.c. It resembles the resin of jalap (*convolvulin*), and corresponds to it in chemical properties. *Fixed oils*, 12 p.c., mucilage, tannin.

Dose.—30 to 45 grs. or 2 to 3 grms.

Preparations

1. **Pulvis Kaladanæ Compositus.**—Kaladana, 3; acid potassium tartrate, 6; ginger, 1. *Dose.*—10 to 60 grs. or 0.6 to 4 G.
2. **Tinctura Kaladanæ.**—1 in 5. *Dose.*—½ to 1 dr. or 2 to 4 mils.

KALADANAE RESINA

Syn.—Pharbitisin.

Source and characters.—A mixture of resins obtained from Kaladana. In brownish opaque fragments, translucent at the edges; brittle, breaking with a resinous fracture of a disagreeable odour, specially when warmed.

Dose.—2 to 8 grs. or 0.12 to 0.5 G.

Pharmacology and Therapeutics

The action and uses of Kaladana and its resin are the same as those of jalap (*see* page 349), but it is a milder remedy. In small doses it is a gentle purgative, but in large ones, especially in the form of Pulv. Kaladanæ Co., it has a drastic action and can be used with benefit in all cases of dropsy.

Diuretics

BOERHAAVIA DIFFUSA

Syn.—Punarnava.

Source.—The fresh or dried leaves.

Composition.—(1) An alkaloid *Punarnavine*, 0.01 p.c.; (2) potassium nitrate, 0.2 p.c.

Preparation

1. **Extractum Punarnavæ Liq.**—1 in 1 of alcohol. Made with fresh or dried plant. *Dose*—½ to 1 dr. or 2 to 4 mils.

Pharmacology and Therapeutics

Punarnava has been used in India as a remedy for dropsy from time immemorial. But only recently a thorough investigation of the drug has been done. Intravenous injection of the alkaloid produces a distinct and persistent **rise of blood-pressure** and a marked **diuresis.** The diuresis is chiefly due to the action of punarnavine on the renal epithelium, and partly to the rise of blood-pressure. The presence of a large amount of nitrate of potassium contributes to the diuresis when the liquid extract is used. It is very valuable in cases of **dropsy** due either to **cirrhosis of the liver,** or when **associated with kala-azar,** and **ascites** due to chronic peritoneal conditions. It is not of much value in cardiac dropsy or in chronic nephritis when given alone, but combined with other diuretics it increases the amount of urine. It loses its action after a few days when its use should be stopped.

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Urinary Antiseptics

CUBEBAE FRUCTUS

Syn.—Cubebs ; *Kabab chini*, Beng.

Source.—The dried full-grown unripe fruits of *Piper Cubeba.*

Composition.—(1) The *volatile oil*, 10 to 18 p.c. (2) *Cubebin*, a neutral body. (3) A resin containing *cubebic acid.* (4) *A fatty oil.* Gum.

Dose.—30 to 60 grs. or 2 to 4 grms.

Preparations

1. **Oleum Cubebæ.**—A pale green, greenish-yellow or colourless oil, smelling of cubebs, distilled from cubebs. Sp. gr. 0.910 to 0.930. *Dose.*—5 to 20 ms. or 0.3 to 1.2 mil.

2. **Tinctura Cubebæ.**—1 in 5. *Dose.*—½ to 1 dr. or 2 to 4 mils.

Pharmacology

Externally.—The action of cubebs depends upon the oil and the resin which it contains. It causes **rubefaction** when rubbed into the skin.

Internally. **Gastro-intestinal tract.**—Here the action of cubebs resembles that of pepper. In small doses it is a **stimulant, stomachic** and **carminative**, and in large doses it **impairs digestion.** In still larger doses it causes **gastro-intestinal irritation.**

Respiratory and genito-urinary tracts.—Like many oleoresins, cubebs enters the blood and is carried to different tissues and organs, upon which it acts more or less like copaiba. It **stimulates** the **secretions** of the mucous membranes of the **respiratory** and **genito-urinary passages** and renders them aseptic. It also stimulates the action of the kidneys, and to some extent that of the skin. It is therefore a **diuretic** and **genito-urinary antiseptic.**

Elimination.—It is chiefly excreted in the bronchial secretion and urine, and is probably found in the latter in the form of a salt of cubebic acid, which may be precipitated by HNO_3. Many of the specific germs are destroyed by the products of the volatile oil as they pass out.

Therapeutics

Internally.—Unlike copaiba, cubebs is often used in the form of lozenges or inhalation to relieve **cough, cold** and **sore-throat.** On account of its specific action on the genito-urinary passages, it is largely employed with copaiba in acute or chronic **gonorrhœa, gleet** and **cystitis.**

Prescribing hints.—The powdered cubebs may be given in lozenges, cachets, or as a paste with copaiba, and the oil in capsules, or in emulsion, often with copaiba, buchu, etc.

Antiperiodics

BERBERIS

Syn.—*Daruharidra kasta*, Beng. *Darhald*, Hind.

Source.—The dried stem of *Berberis aristata.*

Composition.—The chief alkaloids are (1) *Berberine*, and (2) *Oxycanthine*, tannin, resin, gum, etc.

Preparations

1. **Tinctura Berberidis.**—1 in 10. *Dose.*—½ to 1 dr. or 2 to 4 mil.

2. **Ext. Berberidis.**—An impure watery extract from the wood and bark of several species of berberis sold in the Indian bazaars under the name of **Rasot,** which can be purified by dissolving it in alcohol (90 p.c.) and evaporating it to a pilular consistence. *Dose.*—30 to 60 grs. or 2 to 4 grms.

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3. **Berberine Carbonate, Hydrochloride, Phosphate** and **Sulphate,** are yellow crystals more or less soluble in water. *Dose.*—1 to 5 grs. or 0.06 to 0.3 G.

Pharmacology and Therapeutics

Externally.—Being a mild **local astringent** *rasot* is employed with benefit as a pigment around the eyes in acute and chronic **ophthalmia.** Gupta and Dikshit have shown that berberine in dilution of 1 in 80,000 is toxic to **Leishmania tropica,** in which condition it has been used successfully either in the form of *Rasot,* or berberine sulphate 1 c.c. of a 1 to 2 p.c. solution may be infiltrated into the margins of the sores by means of a fine hypodermic syringe, once a week.

Internally.—Berberine is a stimulant to the gastro-intestinal tract, and acts as a **stomachic tonic** in small doses. It is a **diaphoretic** and **antiperiodic** and has been used in the treatment of malaria, either alone or in combination with quinine. It is doubtful, however, whether it has any specific effect on the parasites, and the results have been disappointing. It however helps to expel the parasites into the peripheral circulation and acts as a provocative agent in the diagnosis of malaria.

Given intravenously the alkaloid causes a fall of blood-pressure from dilatation of the splanchnic vessels and cardiac depression.

ALSTONIA

Syn.—Dita Bark. *Saptaparna,* Sans. *Chatim,* Beng. *Chatian,* Hind.

Source.—The dried barks of *Alstonia scholaris* and of *Alstonia constricta.*

Composition.—The bark contains many alkaloids the chief being *ditamine, echitamine* or *ditaine* from the *dita bark* (*A. scholaris*), and *Alstonine* and *porphyrosine* from the bark of *A. constricta.*

Preparations

1. **Infusum Alstoniæ.**—1 in 20. *Dose.*—½ to 1 oz. or 15 to 30 mils.
2. **Tinctura Alstoniæ.**—1 in 8. *Dose.*—½ to 1 dr. or 2 to 4 mils.

Pharmacology and Therapeutics

The bark is an astringent, tonic, antiperiodic and anthelmintic, being considered very useful in chronic **diarrhœa,** advanced stages of **dysentery** and **catarrhal fevers.** Ditaine paralyses the motor nerve-endings in mammals. It has been used successfully in the treatment of **malarial fever.** Dr. Sharp used the bark of *A. constricta* in certain conditions of **typhoid fever,** and **influenza** after its febrile stage and considers it to be an excellent **tonic** possessing the combined properties of quinine and strychnine.

PICRORHIZA

Syn.—*Kutki, Katki,* Beng., Hind., *Katuka,* Sans.

Source.—The dried rhizome of *Picrorhiza Kurroa.*

Composition.—(1) bitter glycoside, *Picrorhizin,* yielding as its decomposition product *picrorhizetin* and *dextrose.* (2) Cathartic acid. (3) Gum, etc.

Dose.—10 to 20 grs. or 0.6 to 1.2 grm. as a tonic; 45 to 60 grs. or 3 to 4 grms. as an antiperiodic.

Preparations

1. **Extractum Picrorhizæ Liquidum.**—1 in 1 of alcohol (60 p.c.). *Dose.*—15 to 60 ms. or 1 to 4 mils.
2. **Tinctura Picrorhizæ.**—1 in 4. *Dose.*—½ to 1 dr. or 2 to 4 mils.

Pharmacology and Therapeutics

The root is bitter and stomachic and is often used whenever a bitter is indicated, as in **dyspepsia** and **neuroses** of the stomach

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and bowels. It is an **antiperiodic**, and is used in malarial fever in place of, or with, quinine. Because of the presence of cathartic acid it acts as a gentle cathartic when given alone, and in large doses acts as a purgative. As a remedy for **bilious fever** *kutki* is often combined with various aromatics and *neem* bark.

Volatile Oils

BETEL

Syn. I.V.—*Pan*, Beng. *Pan, Tambuli*, Hind.

Source.—The leaves of *Piper Betle.*

Composition.—(1) Two *aromatic oils*, light and heavy, which treated with caustic potash yield *chavicol*, a phenol having powerful antiseptic properties. (2) An alkaloid, *arakene*, with properties somewhat allied to cocaine. (3) *Betel phenol* (chavibetol), a phenol.

Pharmacology

Externally.—Dry betel-leaf has no action. Fresh betel leaf is a gentle **stimulant** to the skin, due to the volatile oil it contains.

Internally.—When chewed, the fresh leaf, because of the presence of volatile oil, is a mild **sialagogue**, allays thirst and dryness of the mouth. It also removes foulness of the breath. Reaching the stomach the juice produces a sensation of warmth and acts as a mild **stomachic** and **carminative**, at the same time gives a feeling of well-being. It is a mild **astringent** and **expectorant**. The warm juice is considered a **febrifuge**. Too much chewing of *pan* blunts hunger, probably because of the presence of the alkaloid arakene. If taken in excess it may cause intoxication somewhat similar to that of alcohol.

It has been suggested that it excites sexual impulses but there is no definite proof.

Therapeutics

Externally.—As an easily available domestic remedy, betel leaf is used for various purposes. Smeared with mustard oil or *chunam* (hydrated slaked lime) and warmed, it is applied to the temples in **headache**, to the neck in **sore-throat**, to **swollen glands** to promote their absorption, and to the breasts to check the secretion of milk. In catarrhal and pulmonary affections of children, the leaves smeared with oil and warmed are applied in layers to the chest, when they relieve both cough and dyspnœa. The leaves may be similarly employed in **hepatitis, orchitis, ovaritis**, etc. The Bengal betel leaves are most valuable in these cases. They are used as dressings for foul ulcers, or as substitutes for oiled silk or gutta-percha tissue. The juice is sometimes dropped into the eye in **ophthalmia** or into the ear (warmed) to relieve **earache**. The stalk of the leaf smeared with oil is introduced into the rectum in **constipation** and flatulence of infants.

Internally.—The people of India chew prepared *pan* which is made by wrapping slices of areca nut (*Areca catechu*) with a proportionate quantity of catechu, chunam (hydrated slaked lime) and spices in betel leaves. This combination is very efficacious in **ulcerated** and **spongy gums**, and as a digestive adjuvant in **dyspepsia**. Prepared *pan* is an excellent masticatory for removing the after-taste of bitter and nauseous drugs, and dryness of the mouth in Bright's disease and diabetes. The juice may be given as an expectorant in **colds** and **cough**, or as an **antipyretic** in the **catarrhal fever** of children.

OLEUM AJOWAN

Syn.—Ptychotis Oil. *Jowaner tel*, Beng. *Ajowan ke tel*, Hind.

Source.—The oil distilled from the fruit of *Carum copticum.*

Characters.—Colourless, odour and taste of thyme: sp. gr. 0.910 to 0.930. If

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cooled to 15.5°C. should yield not less than 40 p.c. of crystalline *thymol*, known in the Indian bazaars as *ajowan ke phool*.

Pharmacology and Therapeutics

Internally.—The action and uses of the oil resemble those of thymol (*see* page 519). The fruit when chewed is a capital remedy for removing the nauseous taste of drugs and the oil for correcting the griping of purgatives. **Omum water** or *ajowan ke arak*, distilled from the fruits, is a valuable **carminative** and **antispasmodic** in **colic** and **flatulent dyspepsia.** Ajowan is often chewed with *pan*, or taken with salt for indigestion.

PSORALEA CORYLIFOLIA

Syn.—*Babchi*, Beng.

Source and characters.—The seeds are brownish-black, 2 mm. long flattened and oblong. Odour, aromatic; taste, bitter, pungent.

Composition.—An *essential oil*, a fixed oil, and a resin.

Action and Uses

It has been used as a remedy for **leucoderma**, and within recent years its use has been revived by Acton, who found the oleo-resinous extract (which contains most of the volatile oils) a suitable preparation, which is rubbed over the diseased patches. It is of no use in leucoderma of syphilitic origin.

Astringents

MYROBALANUM

Syn.—Chebulic Myrobalans. *Haritaki*, Beng. *Hara*, Hind.

Source.—The dried immature fruits of *Terminalia Chebula*.

Composition.—(1) *Tannic acid*, about 20 to 40 p.c. (2) *Gallic acid*. (3) Resin, etc.

Dose.—30 to 60 grs. or 2 to 4 grm.

Preparations

1. **Unguentum Myrobalani.**—1 in 5 of benzoinated lard.
2. **Unguentum Myrobalani cum Opio.**—7.5 p.c. of opium.

Pharmacology and Therapeutics

These fruits were highly extolled by the ancient Hindu physicians as powerful **astringents, stomachics,** and **tonics.** The finely powdered fruit forms an important ingredient of tooth powder. It is also a valuable remedy for **spongy** and **ulcerated gums.** Paradoxical as it may appear the dried unripe fruit acts as a gentle **laxative.** One or two fruits taken daily at bed-time keep the bowels very regular, giving one or two evacuations in the morning. On account of the astringent and aperient properties, myrobalans, especially the smaller variety (*Jangi haritaki*), are very useful in **diarrhœa** and **dysentery.** Owing to the large amount of tannin which they contain, they are of great service as **lotions** and **injections** and may be substituted with advantage for **galls.** The ointment is a valuable application in piles. They may also be chewed with benefit to remove the after-taste of nauseous drugs. *Jangi haritaki* fried in a little good *ghee*, and then soaked in the sun for about a week with lime juice and black salt, is a well-known domestic remedy.

KURCHI CORTEX

Syn.—Conessi Bark. *Kurchi*, Beng. *Kutaja*, Sans.

Source.—The dried bark of *Holarrhena antidysenterica*.

Composition.—The seed and the bark contain three alkaloids (1) *Kurchicine* or

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Conessine, an amorphous powder, soluble in water and alcohol and in dilute acids. (2) *Holarrhenine*. (3) *Kurchine*. Also contains tannin.

Dose.—4 to 10 grs. or 0·25 to 0·6 grms.

Preparations

1. **Extractum Kurchi Liquidum**.—1 in 1 of alcohol. *Dose*.—1 to 2 drs. or 4 to 8 mils.

2. **Infusum Kurchi**.—1 in 10 of boiling water. *Dose*.—1 to 2 ozs. or 30 to 60 mils.

3. **Kurchi Bismuth Iodide**. *Syn*.—*Anabin*; *Kurchibine*.—Contains total alkaloids 27 p.c., bismuth 22.85 p.c., iodine 50.15 p.c. *Dose*.—4 grs. twice a day for two weeks.

Action and Uses

Kurchi is a well known remedy for the treatment of **dysentery** both acute and chronic. It acts by virtue of the alkaloid *kurchicine* which has a specific action on *E. hystolitica*. Before the value of ipecacuanha was recognised in dysentery it was the only remedy extensively used in India. It may be given alone, either in the form of liquid extract or as fresh infusion, or may be combined with small doses of castor oil, extract of bael or decoction of ispaghula, or the seeds (*indrajab*) may be given in the form of powder with powdered ispaghula seeds. Kurchicine may be used subcutaneously in $\frac{1}{5}$ to 1 gr. doses, but as it depresses the heart and makes it irregular it cannot be used intravenously. It has the advantage over emetine in being useful also in **bacillary dysentery**. It has no effect on the pregnant uterus in therapeutic doses and therefore may be given safely during pregnancy (Chopra). Kurchi-bismuth-iodide is now used in cases of chronic intestinal amœbiasis with better results than with pure kurchi preparations, and has the advantage over similar preparations of emetine in not being a depressant. The alkaloid may be used in the same conditions and is free from any cumulative effect. Sometimes flushing of the face and extremities, giddiness, and buzzing of the head occurs, but these pass off on reducing the dose or stopping it for a few days. It may be given in capsules or as tablets. (Acton and Chopra).

Kurchicine is an **antiperiodic** and may be used by the mouth (2 to 5 grs.) with benefit in cases of dysentery complicated with fever.

Anthelmintics

BUTEAE SEMINA

Syn.—Butea Seeds: *Palas Bij*.

Source.—The seeds of *Butea frondosa*.

Composition.—Fat 18 p.c., albuminoid substances 19 p.c., and glucose. The fat exists in the form of *moodooga* oil.

Preparation

1. **Pulvis Buteæ Seminum**.—The kernel dried and powdered, freed from the testa after soaking in water. *Dose*.—10 to 20 grs. or 0.6 to 1.2 grm.

Pharmacology and Therapeutics

Externally.—The seeds made into a paste with lime-juice act as a **rubefacient** and may be used in ringworm. The leaves may be used as a poultice to disperse boils, pimples, buboes and hæmorrhoids.

Internally.—The seeds are powerful **anthelmintic** for **round-worm** and may be used as a substitute for santonin, followed as usual by a dose of purgative

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CUCURBITAE SEMINA PRAEPARATA

Syn.—Red Gourd Seeds; Pepo; Melon Pumpkin Seeds; *Bilati Kumrar bij*, Beng. *Mitha-kadu ke bij*, Hind.

Source.—The prepared fresh ripe seeds of cultivated plants of *Cucurbita maxima*.

Composition.—(1) A *resin*, fixed oil, 30 p.c., sugar, starch, etc.

Dose, U.S.P.—30 grms. or 1 oz.

Pharmacology and Therapeutics

Internally.—Both the seed and the oil are efficient **anthelmintics** for **tape-worm.** The former is best given bruised with a little water or milk on an empty stomach early in the morning, followed by a simple purgative at 10 A.M., the latter in ½ oz. doses repeated at an interval of 2 hours and then followed by an aperient.

EMBELIA

Syn.—*Biranga*, Beng. *Baberang*, Hind. *Vidanga*, Sans.

Source.—The dried fruit of *Embelia Ribes*, and of *Embelia robusta*.

Composition.—(1) *Embelic acid* or *embelin* 2.5 p.c. (2) An alkaloid *Christembine*, resin and tannin.

Dose.—1 to 4 drs. or 4 to 16 grms. (in powder).

Pharmacology and Therapeutics

These berries are considered a valuable **anthelmintic** for **tape-worm**, and may be used in powder or as infusion (without straining). The taste is not unpleasant and the directions are the same as those given for the administration of melon pumpkin seeds.

Demulcents

ISPAGHULA

Syn.—Spogel Seeds. *Isaphgul*, Beng.

Source.—The dried seeds of *Plantago ovata*.

Composition.—(1) *Mucilage*, 1 in 20 of water forms a thick tasteless jelly. (2) *Fixed oil* and albuminous matter.

Dose.—45 to 150 grs. or 3 to 10 grms. (in powder).

Pharmacology and Therapeutics

Externally.—The bruised seeds, moistened with water, form an excellent, emollient poultice, and can be used for the same purposes as linseed. When made with vinegar and oil they are applied over rheumatic and gouty swellings.

Internally.—Isaphgul is a **demulcent** and mild **laxative** acting like agar-agar by virtue of its bulk. Like the seeds of *Plantago Psyllium*, it is used for correcting constipation. Two to three teaspoonfuls of powdered seed taken at bed-time with a little sugar and water give one or two clear evacuations without any griping in the morning. When soaked in water (1 in 40) it forms a mucilaginous mass which acts as a protective layer over the intestinal mucous membrane, and is used as a domestic remedy in **acute** and **chronic dysentery.** The mucilage also inhibits the growth of bacteria in the intestine and adsorbs toxins, thus preventing their absorption. It is often combined with bruised *kurchi seeds* (*Holarrhena antidysenterica*), commonly known as *Indra-jab*, the dose is 5 grs. every two or three hours, and this combination will be found to yield most encouraging results. The decoction is also used as a demulcent in **cough** and **sore-throat,**

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and formed into a *sherbet* (seeds, sugar and water) it is larely used as a cooling beverage in **gonorrhœa**, when it acts as a mild diuretic and soothes the irritation of the urethra during urination.

The remedy is tasteless and is well suited both to adults and children.

AGROPYRUM

Syn.—Triticum ; Couch Grass.

Source.—The dried rhizome of *Agropyrum repens*, freed from remains of leaves and rootlets.

Characters.—Rhizome pale yellow, rigid, from 2 to 2½ mm. in diameter, usually in pieces from 3 to 6 mm. long. Furrowed longitudinally, hollow except at the nodes. No odour Taste, faint sweetish.

Composition.—(1) *Triticin* resembling inulin. (2) *Glucose, mucilage, mannite, inosit.* No starch.

Preparations

1. **Decoctum Agropyri.**—1 in 20. *Dose.*—½ to 2 ozs. or 15 to 60 mils.
2. **Extractum Agropyri Liquidum.**—*Dose.*—1 to 2 drs. or 4 to 8 mils.

Pharmacology and Therapeutics

Internally.—It is a **demulcent** and **diuretic**, being largely employed in **cystitis** and **irritation of the urinary passages.** The decoction well diluted may be employed as a diluent. Only the fresh rhizome possesses these properties, the dried one is inert.

Cardiac Tonnic

TERMINALIA ARJUNA

Syn.—Arjuna ; *Arjun.*

Action and Uses

The bark of this tree possesses a reputation of being a valuable **cardiac tonic** and is extensively used in this country for all sorts of cardiac troubles and complications. The bark was subjected to careful analysis in the *Pharmacological Laboratory of the Carmichael Medical College* and was found to contain (*a*) *tannin* about 12 p.c. mainly of pyrocatechol nature ; (*b*) soluble salts of *calcium, magnesium* and *aluminium*, 22.4 p.c. ; (*c*) an *organic acid* of high melting point ; (*d*) *colouring matter* ; and (*e*) *sugar.*

The reputation of the drug and the fact that it is extensively used and advertised as a cardiac tonic led us to make a careful investigation of its action on animals. The observations of Chopra were negative, although it is possible that the high calcium content may have some effect on the cardiac muscle. Experiments made with liquid extracts obtained from the reputed manufacturers and prepared in the laboratory show that it causes a **fall of blood pressure** in intact animals even in very small doses ; while larger doses cause death of the animal from stoppage of the heart. On isolated heart the beats were rendered weaker and eventually the heart stopped from direct action on the cardiac muscle. These findings are directly opposite to the general belief. Further work is necessary to substantiate these observations.

Antiseptic

AZADIRACHTA INDICA

Syn.—Neem Bark ; Margosa Bark.

Source.—The dried bark of the stem of *Melia azadirachta.*

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Composition.—(1) A *bitter amorphous resin.* (2) *Margosine*, a bitter alkaloid. (3) *Margosic acid.*

Preparations

1. **Infusum Azadirachtæ Indicæ.**—1 in 100. *Dose.*—½ to 1 oz. or 15 to 30 mils.
2. **Tinctura Azadirachtæ Indicæ.**—1 in 10. *Dose.*—½ to 1 dr. or 2 to 4 mils.
3. **Margosic Acid.**—A mixture of fatty acids of the oil derived from the seeds.
4. **Sodium** and **Potassium Margosates.**—Valuable in combating infections of diverse nature in many forms of skin affections. Injections are said to be useful in *leprosy.*

Pharmacology and Therapeutics

Externally.—The leaves in the form of a decoction or poultice are largely employed to **stimulate foul** and **indolent ulcers** to a healthier action. The decoction is also used as an antiseptic lotion or a general bath in many skin diseases. Obstinate ulcers have been cured by neem-poultice. Weeping **eczema** quickly heals if a cold poultice of the bruised leaves is applied and allowed to remain till it drops off.

The oil extracted from the seeds is a valuable local **stimulant, antiseptic** and **bactericide.** Alone or in combination with chaulmoogra oil or gurjun balsam, it is considered to be an effective application in **leprosy.** Injections of margosates and the local application of the acid have been found to be of greater value in the treatment of **leprosy** and **syphilitic conditions** than the oil.

Internally.—The bark is a **bitter tonic, astringent** and **antiperiodic,** the astringent properties residing in the outer layers. Before the introduction of quinine into this country, the bark either in powder (1 dr.) or in concentrated decoction, was largely employed in **malaria.** Its decoction is employed even now in many cases of malarial fevers where quinine fails to effect a cure, or as a tonic during convalescence. The root bark possesses **anthelmintic** properties.

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PART VII

PHARMACY AND DISPENSING

GENERAL DIRECTIONS

1. **The dispensing room** must be well *lighted* and well *equipped* with every necessary article, furniture and apparatus for compounding and dispensing purposes.

2. **Pure drugs of the best quality** are to be used, and preparations are to be made in strict accordance with the *official* and other *recognised methods.*

3. **Bottles are to be duly labelled.**—Those containing corrosive fluid must have *enamelled inscription,* or names engraved on glass. Bottles containing **poisonous** substances must bear an extra label—"**Poison**"—at their shoulders. It is a good plan to have also the *doses* printed on the labels.

4. **Poisonous drugs** must be kept within a separate glass case under lock and key.

5. **The counter and the apparatus** for compounding and dispensing must be kept scrupulously clean, in good order, and ready for immediate use. Always clean and put away every article in its proper place after use.

6. **Testing of drugs** must be done occasionally so as to ensure their purity and strength. Substances like vegetable extracts, spirit of nitrous ether, hydrocyanic acid dilute, etc., require occasional looking after.

7. **Corks of good quality** should be used. Cracked, old, rotten and soiled corks should be rejected. The practice of pressing corks between the teeth should never be indulged in. Fit a cork before pouring the medicine into the bottle.

8. **Evidence of slovenliness** as regards externals does not encourage faith as to the care with which the contents have been dispensed.

9. **Prescription reading.**—Read through a prescription calmly and rapidly, without creating any suspicion in the mind of the presenter, but noting at the same time any inconsistency either in dosage or in combination.

10. **Consultation with the prescriber** must be arranged without delay, whenever possible, if there is any **poisonous** or **unusually large dose,** or a grave **incompatibility** in a prescription. The dispenser should on no account alter a physician's prescription without his sanction.

11. **The directions** on the label should be written first of all before the medicine is dispensed. At the same time the prescription should be copied in the copy-book, noting afterwards any peculiarity of compounding or dispensing. If the directions are in Latin, the dispenser should give their English translation. In India, the directions should be written in the familiar language of the place, when the medicines dispensed are meant for those who cannot read English.

12. **Labels** should be neatly and distinctly printed without much flourish, and their margins carefully trimmed. "**Poison,**" "**Shake the bottle,**" "**Not to be taken**" and other accessory labels are best placed on the **shoulder** of a bottle. If affixed at the foot, the fingers holding the bottle may cover them, or a hurried patient may overlook them. The colour of labels for liniment and lotion ought to be different from that of mixture and powder. Orange-red and dark-yellow for the former and white for the latter may be used. Sometimes the labels for liniment and lotion are printed with red on white paper.

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13. **Bottles for dispensing** mixtures should be of a different colour from those used for liniments and lotions. Amber-coloured or uranium bottles are best suited for silver nitrate lotions, and blue bottles for liniments. Bottles covered with blue paper can be used for silver lotions, when uranium or amber-coloured bottles are not available.

14. **The dispensing of two prescriptions simultaneously** should never be attempted. But if an infusion is to be made the dispenser may set it on, noting on a bit of paper the time and the substance, and placing it between the cover and the pot.

15. **The position of a prescription during dispensing** must be such that the dispenser can read it while dispensing. This can be best accomplished either by fixing it to a hook on a counter-shelf, or by holding it between the index and the middle fingers of the left hand.

16. **Manipulation.**—Be expeditious in manipulation. Finish tying, sealing, labelling and wrapping as quickly as possible. The holding of powder envelopes between the lips, the handling of drugs, the stirring of mixtures with the fingers is to be avoided.

17. **The final reading of a prescription** is essential before the medicine leaves the hands of a dispenser, so as to make a revision of his work. If there is any doubt, always begin where there is none.

18. **Graduations of bottles** must be accurate. Want of symmetry of the bore makes a great deal of difference. Blown lines of graduation are generally wrong. Paper graduation is the best, but it must be done by hand in each case. Mark-papers should either be notched or lined equidistantly, but in either case the number of doses should be put down in figures on the label.

19. **Repetition of prescription.**—If a prescription contains such drugs as are likely to produce a cumulative effect, or a habit, as strychnine, arsenic, lead, digitalis, opium, etc., the dispenser should warn the patient against repeating it for a lengthened period without the knowledge and sanction of the prescriber. To prevent indiscriminate renewals of medicine containing poisonous ingredients, the physician should write "*non-repetatur*" or some similar direction on his prescriptions.

WEIGHING AND MEASURING

1. **Scale.**—An upright fixed beam and scale with a movable glass pan should be used. If a hand scale is used, hold it firmly by the left hand, never lift it too high above the counter, and judge the weight as much by the indicator as by the position of the scale. A delicate scale should be used for weighing minute quantities of powerful drugs; such as strychnine, hyoscine, arsenic, etc.

2. **Corroding substances.**—Substances which corrode or act on the brass should be weighed upon glass pans. Crystallised acids, iodine, carbonate of ammonia and similar salts should never be weighed on brass pans.

3. **Soft or sticky substances**, such as soft extracts, confections, ointments, etc., should be weighed on a piece of paper spread over the right pan, after placing a corresponding piece of equal weight on the left along with the weights. Scrape the medicine by a spatula from the paper after weighing.

4. **No guesswork** in weighing or measuring is allowed. Every drug must be either weighed or measured.

5. **Label upwards.**—In pouring out liquids, always keep the label of the bottle upwards in order that it may not be spoiled by the trickling down of the drops of liquid left on the lip of the bottle.

6. **Minim measure.**—From a few drops to a drachm, the liquid should be measured in a minim glass. The true level of the surface of the liquid in a minim glass is the midway between the highest point close to the glass and the lowest at the centre.

7. **Lip drops.**—The drops that hang from the lip of a bottle out

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of which a liquid has been poured, should be caught upon the bottom of the stopper, before putting it back into the mouth.

8. **How to drop.**—Before permitting drops to fall into any mixture, the dispenser must allow a few drops to fall on a separate vessel till he is confident that he has a perfect control over dropping. If he is not sufficiently skilful, let him measure the drops into an empty glass until he is satisfied that he has obtained the correct number.

9. **Volatile liquids,** such as, ether, chloroform, nitrite of amyl, dilute hydrocyanic acid, etc., should always be measured instead of dropped. A solution of 10 or 20 per cent. may always be kept in stock for measuring out small quantities when ordered.

10. **The size of drops** varies considerably, and therefore it is safe to give *minims* where *guttæ* are ordered. Thus, chloroform dropped from an ordinary phial will require 150 to 300 drops to one fluid drachm.

11. **Division of a grain or a minim** is best accomplished by triturating or mixing the weighted or measured quantity with sugar of milk or any liquid excipient, and dividing the mixture as ordered. For instance, suppose that 24 pills are ordered, each containing $\frac{1}{30}$ grain of strychnine hydrochloride. The total amount in the 24 pills will be $\frac{24}{30} = \frac{4}{5}$ grain, therefore weigh out 1 grain of the salt and triturate it with 4 grains of milk sugar, making 5 grains in all. Then 4 grains of this mixture will contain $\frac{4}{5}$ grain of strychnine hydrochloride. Take this amount and destroy the remainder.

WATERS

1. **Camphor water.**—2 ozs. of water dissolve only $\frac{1}{12}$ gr. of camphor. The easiest way of making a good camphor water is to mix flowers of camphor with coarsely powdered glass, enclose and tie the mixture in a muslin bag and suspend it by a thread into the water from the cork. A good solution is obtained sooner by moving the bag up and down two or three times a day.

By dissolving $2\frac{1}{2}$ drs. of spirit of camphor in 40 ozs. of water, camphor water may be quickly obtained.

2. **Chloroform water** is made by the simple shaking of chloroform in water.

For the preparation of **aromatic waters,** B. P., *see* page 17.

DECOCTIONS

1. **Drugs** should be coarsely powdered or sliced before they are boiled in water for 5 minutes or longer. If the comminution is too fine some sediment deposits. The drugs should always be put in cold water before boiling.

2. **Decoction pots** should be enamelled or tinned and covered. A false bottom made of tinned or silver gilded copper wire half an inch or more above the bottom should be used to prevent imparting a fusty odour to the decoction from the particles of the drug adhering to the bottom of the vessel during boiling.

INFUSIONS

1. **Drugs for infusion** should not be too finely comminuted.

2. **No other water than distilled water,** boiling or cold, is to be used.

3. **Suspension of drugs** is essential. A muslin bag containing the drugs can be suspended by a thread from the lid of a covered pot, or a Squire's or Maw's infusion pot may be used.

4. **Uniform temperature,** as far as possible, should be maintained.

5. **Hard spring water** does not give a good colour, as the extractive matters are not well dissolved by it.

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6. **Infusions** should be made **fresh** and these are now named in the Pharmacopœia as fresh infusions as distinguished from **concentrated infusions** introduced in the new B.P., which after dilution resemble the fresh infusion. The concentrated infusion of digitalis is not sanctioned in the new B.P. and should not be used, as it is inactive.

EMULSIONS AND MIXTURES

Emulsion, as its name implies, is a liquid externally resembling milk, the milkiness being due to the suspension of resinous or oily bodies in water, by means of an adhesive substance known as the *emulsifier* or *emulgent*. Emulsion therefore is a mixture of two liquids which are insoluble in each other. The emulsifier helps the insoluble substance to remain finely divided or broken up in the form of globules which do not coalesce again to form a separate unmiscible fluid.

Emulsions are prescribed (*a*) to help administration of oily substances which will not mix with water; (*b*) to help easy absorption of the oily substance which is presented in a finely divided and dispersed state in some vehicle; and (*c*) to make it more palatable.

1. **The first fundamental rule** *in the compounding of a mixture is to avoid chemical decomposition taking place among its ingredients, unless such is the implied intention or the express order of the prescriber.*

2. **Distilled water** should be used in compounding. Tap or other waters produce a considerable change in mixtures owing to the presence of traces of calcium and magnesium salts. For example, Tinct. Card. Co. produces a brilliant crimson colour with tap, and a reddish-brown with distilled water. Tinct. Lavand. Co. gives a bright mixture with distilled, and a muddy one with tap water. Ordinarily the word "aqua" means tap water. If the prescriber wants distilled water to be used he should write "aqua destillata".

3. **Order of mixing.**—It is not the spirit of practical pharmacy to mix the ingredients in the order in which they are written in a prescription. The dispenser should exercise his own judgement in determining the best method of effecting a combination.

It is a good plan first to pour in the tinctures and spirituous fluids as they are measured, next add syrups and essences, and lastly fill up the bottle with the vehicle.

4. **Poisonous drugs** such as arsenic, strychnine, perchloride of mercury, hydrocyanic acid dilute, etc., should be separately dissolved and then added to the mixture last of all, immediately before corking the bottle. In this way you avoid the possibility of putting them in twice over.

5. **Mortar and pestle** should never be used if the ingredients are easily soluble. Dispense syrups and fluid preparations in such an order that the vehicle will finally rinse out the measure glass.

6. **Shaking.**—All mixtures should be briskly shaken before labelling, to ensure a thorough incorporation of the ingredients.

7. **Heat** should not be used to help the solution of salts when they will not entirely dissolve in cold water, for they are sure to crystallise on cooling. Suspension is the best method under such circumstances.

8. **Wholly or partially soluble vegetable drugs**, especially which contain tannin, should be *mixed with earthy and metallic salts in largely diluted solutions.*

9. **Gelatinous mixtures.**—Some mixtures become *gelatinous* on keeping, due to the growth of an organism called *viscous ferment.* An addition of 20 per cent. of alcohol to the mixture prevents this.

10. **Chemical reaction.**—If there is a chance of a chemical reaction taking place, the ingredients which are likely to act with one another,

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should be freely and separately diluted or suspended, before mixing. The mucilage of acacia always suspends the precipitate uniformly, and to some extent retards or modifies the chemical decomposition.

11. **Froth.**—Sometimes a lot of froth rises as the result of shaking, especially if the mixture contains vegetable solutions, thus preventing the bottle from being filled or corked. A few drops of alcohol remove this.

12. **Insoluble powders**, such as rhubarb, chalk, etc., should be triturated with a small quantity of water in a mortar to produce a thin paste, before mixing with the vehicle. No suspending agent should be used by the dispenser unless it is found that equal dosage of the substance is not possible without one. Most of the insoluble powders are easily diffusible and do not require a suspending agent. In any case "shake the bottle" label should be used.

13. **Medicinal filtrates** produced in a mixture should not be filtered, but suspended. But if any foreign particles float on a clear solution, they should be removed either by straining or by filtration through wetted cotton or tow plugged lightly into the neck of a funnel. All mixtures depositing a sediment should bear the label "*shake the bottle*".

14. **Mucilage** should be recently prepared, but it can be kept ready made for some time provided that the bottle containing it is full up to the neck and properly sealed.

15. **Oils** are best emulsified either by rubbing them up with gum or by mixing them with an alkali, or with both. Copaiba is well emulsified with gum and alkali. Essential oils are best emulsified with tragacanth powder in the proportion of 10 grs for every ounce, or yolk of egg.

16. **Scale preparations** in a mixture are either to be dissolved in a mortar with warm water or poured into the bottle with the vehicle, and shaken briskly. If poured in a dry condition into the bottle, and the water or vehicle added afterwards, a sticky mass cakes at the bottom.

17. **Volatile ingredients in a mixture.**—Volatile drugs such as ammonia, ether, chloroform, hydrocyanic acid, etc., should never be mixed with hot fluids, and should always be added last of all, after the vehicle has been poured into the bottle. Care should be taken that sufficient space is left for the requisite quantity of the soluble ingredient. As soon as this has been added, the bottle must be tightly corked and well shaken.

18. **Resinous substances** should first be finely powdered and triturated with mucilage of tragacanth and finally the vehicle is added. They may also be dissolved in alcohol and dispensed in the same way as resinous tinctures.

SUSPENDING AND EMULSIFYING AGENTS

Suspending agents are often necessary to keep insoluble substances in a state of suspension so that each dose should contain a reasonably correct proportion of the compound. If the prescriber does not order any such agent the dispenser should use his own judgement in deciding whether any suspending agent should be used. The following substances are commonly used as suspending agents, viz. acacia, tragacanth, or mucilage of acacia or mucilage of tragacanth, glucose, or syrup.

Mucilage of acacia should be used in the proportion of 1 dr. for each fluid ounce of the mixture. It however has the disadvantage of making mixtures sometimes lumpy, as for instance with bismuth salts, where tragacanth is more preferable and should be used in the same proportion. The following substances require a suspending agent when ordered in a mixture, *viz.* bismuth subnitrate and salicylate, phenacetin and acetanilide, salol, quinine salts (unless an acid is ordered), sulphonal, methylsulphonal, benzoic acid, acid

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acetylsalicylic, barbitonum, and preparations containing resins, e.g. tinctures of podophyllum and asafetida, etc.

There are many *emulsifying agents* and they are almost invariably colloidal substances and thus remain in a state of extreme subdivision in which state its surface area is enormously increased. This state of subdivision demands expenditure of energy, and this energy becomes stored up on the surface of the particles as surface energy, and more finely divided the substance, the greater is its surface area and, consequently, greater its surface energy with greater power to adsorb other substances to its surface.

The emulsifying agents are :—

Acacia powder.—The formation of a good emulsion depends upon right proportion of oil, water and gum. The usual rule is to use one part of powdered gum acacia for every four parts of fixed oil. For volatile oils the proportion is half the quantity of gum as oil. For making emulsion with substances containing oleoresins like copaiba or male fern the proportion should be equal quantity of each.

Powdered gum tragacanth is inferior to acacia, and the oil globules are larger than acacia emulsion and therefore the emulsion with tragacanth is not so white. Gum tragacanth is used more for emulsifying volatile oils and less for fixed oils. The proportion being 10 grs. of the gum for every ounce of the oil.

Yolk of egg is largely used for emulsifying cod-liver oil. It has the advantage over gum emulsion in that it does not separate on the addition of acids, salts, glycerin or syrup. If however the egg-emulsion is kept for long it undergoes putrefaction and imparts a bad odour to the emulsion. Sometimes a little benzoic acid, or 5 p.c. alcohol is added as a preservative.

Alkalies.—The hydroxides of potassium, calcium, ammonium and sodium are generally used. They form soaps by combining with the fatty acids contained in most of the fixed oils of vegetable origin. Volatile oils which do not contain any fatty acids cannot be emulsified with alkalies. Lime water and ammonia are however not used for emulsions intended for internal use. They are largely used for liniments and substances meant for external application.

Soaps.—These are best emulsifying agents for lotions, liniments and other preparations for external use.

Saponins.—These occur in certain substances and form a large amount of froth when shaken with water, similar in appearance to the froth produced when soap is shaken with water. The drugs which contain most saponins are quillaia and senega and the most convenient sources of these saponins for dispensing purposes are the tinctures of the respective drugs. Since both these substances have a therapeutic action of their own they should not be used for making emulsions for internal use unless especially ordered.

MIXTURES AND EMULSIONS OF SPECIAL DRUGS

1. **Acacia** in a mixture is best added in the form of mucilage, which should be freshly made.
2. **Almond oil** does not emulsify well with mucilage or powdered gum, but a small quantity of liquor potassæ or carbonate of potassium without mucilage answers well.
3. **Ammoniacum, Myrrh and Guaiacum** should be triturated first with a little water or some similar vehicle so as to form a thin paste. These do not require a suspending agent as the gum present in these is sufficient to suspend the resin. The resulting mixture may be strained through muslin.
4. **Ammonium Carbonate** should be dissolved in a cold vehicle, only translucent pieces being used. Those portions which have effervesced are wanting in strength.

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5. **Benzoic acid** should be powdered before mixing. If there is a tincture in the formula it should be dissolved in it, and water added gradually with shaking.

6. **Bismuth Carbonate and Subnitrate** are often prescribed in a mixture without any suspending agent. They should first be triturated in a mortar with some of the vehicle to form a paste and then the water should be added to adjust the volume. They are easily diffusible and do not ordinarily require any suspending agent. If any suspending agent is used, acacia should be avoided for reasons explained on page 679. Bismuth subnitrate is chemically incompatible with potassium bicarbonate or sodium bicarbonate, producing a large quantity of carbonic acid gas when mixed in a mixture. $2BiONO_3 + 2NaHCO_3 = Bi_2O_2CO_3 + 2NaNO_3 + H_2O + CO_2$. The gas must be allowed to escape by gentle heat before bottling, otherwise the bottle may subsequently burst or the cork be suddenly blown out. An equivalent quantity of bismuth carbonate may be substituted as the finished mixture contains the same. Bismuth salts and iodides produce bismuth oxyiodide which gives a brownish-red colour to the mixture though therapeutically it is harmless.

7. **Borax** powdered and rubbed up with mucilage makes a soft, jelly-like mass. But a limpid mixture may be obtained by mixing freely diluted mucilage with a solution of borax in warm water.

8. **Butyl-chloral Hydrate** forms oily compounds with alcohol, insoluble in water. Dissolve in glycerin and warm water. **Chloral hydrate** behaves in the same way, and is decomposed by alkalies, liberating chloroform.

9. **Caffeine Citrate** forms a syrupy liquid when mixed with three times its weight of water; on addition of more water, caffeine hydrate is precipitated. This is again redissolved on further dilution.

10. **Camphor** in a mixture is treated with 3 times its weight of alcohol, in the same way as resinous tinctures, *i.e.*, dissolve it in alcohol first and then treat as a tincture. Acacia is a better suspending agent.

11. **Chlorate of Potassium and Hydrochloric Acid.**—Sometimes a formula composed of potassium chlorate, hydrochloric acid, and water comes to the dispenser for dispensing. Here the object is to make a solution of chlorine, and is best fulfilled by adding the acid directly to the salt, corking the bottle for a while before adding water, so as to make a solution of chlorine in water.

Chlorate of potassium with syrup of iodide of iron liberates *free iodine* which has proved fatal.

12. **Cod-liver Oil** is well emulsified by the following method. Place powdered tragacanth in a dry mortar and triturate a little of the oil, then add the yolk of an egg and the oil and stir briskly, adding water as the mixture thickens, and lastly mix flavouring oils and water alternately, with constant stirring, avoiding frothing. The mixing of lime water 1 to 5 with cod-liver oil greatly facilitates its emulsification, and reduces its tendency to cause eructations. Lime water and acacia gum emulsify cod-liver oil just as the yolk of egg.

13. **Copaiba Balsam** can be well emulsified by rubbing it with about its own weight of powdered gum acacia and liqr. potassæ. The resin acids combine with caustic potash and form a soap-like substance which helps emulsification.

14. **Ether** should never be mixed with hot liquids, and must be added last to a mixture.

15. **Ferri Sulph.** soon gives a rusty colour to a solution from the production of ferric hydroxide, which is retarded by adding an acid.

16. **Glycerin** is used as a sweetening agent for mixtures, especially those that contain perchloride of iron. It is also used as an appropriate solvent for, and a preservative of, the pancreatic and peptic ferments. It prevents gelatinisation of kino in tr. kino, and also to a

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certain extent prevents and retards chemical changes and precipitation in a mixture.

17. **Iodine** is very sparingly soluble in water, but iodide of potassium helps solution to the extent of three-quarters of its own weight. Salts of ammonia also increase its solubility by the formation of a soluble salt, ammonium iodide. Some essential oils such as oils of peppermint and fennel, chemically combine with iodine. Strong solution of iodine with solution of ammonia, or with ammoniated camphor liniment, precipitates iodide of nitrogen, which is a most dangerous explosive (*see* Explosive Combinations, page 53).

18. **Morphine Salts** should not be dissolved by heat, for at a temperature above 104° F. their solutions turn yellow or brown.

19. **Paraldehyde** is soluble in water in the proportion of 1 in 10. If it is present in a mixture in excess of its solubility it should be emulsified with tragacanth powder.

20. **Phenacetin** in a mixture requires careful treatment. It should be first finely powdered and then mixed with pulv. tragacanth. co. in the proportion of 2 to 5 grs. for every ounce of the mixture, and then the vehicle added with trituration in a mortar. The same procedure should be followed for **acetanilide.**

21. **Phenazone** is sometimes a troublesome drug to deal with in a mixture. It is rather a free base, and gives precipitate with tannin, alkaloids and many other substances. Thus, with alkaline salicylates it forms *salipyrin* (insoluble) ; with ferric chloride, *ferripyrin* (orange red) ; with free iodine, *iodopyrin* (insoluble) ; with chloral hydrate, *hypnal* (insoluble), etc.

22. **Potassium Iodide** is decomposed by acids, liberating *free iodine*, which may produce fatal results. This also happens when potassium iodide is mixed with tincture of perchloride of iron.

23. **Quinine Salts.**—The following points in respect of the mixing of quinine salts should be noted :—

(*a*) It produces an *insoluble salt* when added to a strong mineral acid; the acid should be freely diluted with the vehicle before the alkaloidal salt is mixed.

(*b*) When it is prescribed with spirit of nitrous ether, tinctures, ether, or any spirituous liquids along with glycerin or syrup and water, the quinine is to be first dissolved in the undiluted spirituous mixture and then glycerin or syrup added, and lastly the vehicle is gradually mixed. If no mucilage is ordered it may be added, to prevent quinine from adhering to the sides of the bottle.

(*c*) The sulphate should not be dissoved in diluted hydrochloric or nitro-hydrochloric acids unless so ordered.

(*d*) When ordered with bark or any other substances containing tannic acid, it deposits a precipitate of tannate of quinine which should not be filtered.

(*e*) No acid should be added by the dispenser to make a solution if it is not prescribed. The quinine is then to be rubbed up in a mortar with a little mucilage and diffused in water, or added to the vehicle in its crystalline state, with "shake the bottle" as a direction. The former is the better method.

(*f*) Quinine salts are *incompatible with alkalies*, such as bicarbonates, carbonates, hydrates, spirit. ammon. aromat., etc. They should be suspended and diluted *separately* before mixing ; a small quantity of mucilage will make a better mixture.

(*g*) Ammoniated solution of quinine gives a precipitate when diluted with water, but the addition of a little mucilage (½ dr. to 1 oz. of mixture) suspends it.

(*h*) With liberated chlorine, quinine salts yield a yellow solution, *i.e.*, when added to the chlorine mixture mentioned in para 11, page 681.

(*i*) Mercuric chloride throws down a poisonous precipitate, which can be dissolved by diluted hydrochloric acid. Glycerin and gum also retard to some extent chemical reaction.

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(*j*) Donovan's solution too behaves in the same way, but an admixture of glycerin and mucilage prevents to some extent chemical changes.

(*k*) When it is ordered with salicylates in a mixture, an ugly-looking mass, salicylate of quinine, forms inside the bottle which refuses to flow out. The mixture may be improved by rubbing mucilage with quinine and gradually mixing the salicylate dissolved in a large quantity of water, and agitating very briskly.

(*l*) Neutral solution of quinine and iodide of potassium do not react chemically, unless there is an acid present, free or liberated, in which case iodine is set free.

(*m*) The growth of fungus in a solution of quinine is prevented by the addition of a 5 per cent. solution of alcohol or a trace of chloroform.

24. **Spirit of Nitrous Ether** turns *acid* due to the fact that the ethyl nitrite becomes hydrolised on keeping with formation of free nitrous acid and should therefore be made *alkaline* before being mixed with iodides or bromides, otherwise free iodine or bromine will be liberated and will darken the mixture. It can be kept permanently alkaline or neutral by dropping a few crystals of potassium bicarbonate in it.

25. **Salol** when combined with other salts in a mixture falls to the bottom in a somewhat granular form; this is prevented by adding compound powder of tragacanth in the proportion of 2 to 5 grs. for every fluid ounce of mixture.

26. **Strychnine** in a mixture containing alkalies is precipitated to the bottom of the bottle, and fatal results may follow the swallowing of the last dose. Bromide and iodide of potassium, liq. hydragyri perchloridi and liquor sodii arsenatis all throw down insoluble precipitates of strychnine compounds.

27. **Tannic acid** should be dissolved in pure distilled water, as tap water makes the solution opalescent. It precipitates alkaloids in solution and gives with iron an inky colour. Alkalies give precipitates, and turn the mixture brown to black. Mucilage makes it flaky.

28. **Vegetable extracts** should be carefully *rubbed* in a warm mortar with a little water till a soft paste is obtained, with which the vehicle is to be gradually mixed. If they are resinous rub them with two or three times their weight of powdered acacia in warm water, and then gradually mix with the vehicle when cold. *Ext. Filicis* may be triturated with its own weight of powdered acacia, and water added gradually with constant stirring.

PILLS

1. **In making a pill-mass**, the following points should be observed:—

(*a*) Put the substance (powder) prescribed in smallest quantity into the mortar first and triturate it with the next smallest (if it is powder), add the next, again triturate, and so on.

(*b*) Toxic substances (*e.g.*, alkaloids and arsenic) should always be triturated well with double their weight of a hard powder (*e.g.*, lactose), if there is none in the pill constituents, before adding the other ingredients gradually.

(*c*) Potent extracts which are prescribed in the pill should not be treated as excipients, *e.g.*, Extr. Nucis Vom. gr. 1/8 with Pulv. Aloes gr. 2, and Pulv. Ipecac. gr. 1/2. Here rub the extract with the ipecacuanha, add a little of the aloes, again triturate, and continue thus until the extract is equally divided throughout the whole.

(*d*) Essential oils should be treated like No. (*c*). Thus in the case of Pil. Aloes, the oil of caraway should be triturated lightly with the powdered soap (the oil being added gradually); then aloes, trituration, aloes, trituration, etc.*

* Chemists' and Druggists' Diary, 1898

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2. **Pills under one grain** should be made up to 1 grain by the addition of liquorice powder or sugar of milk. Fractions of a grain of such powerful drugs as strychnine, perchloride of mercury, arsenic, etc., should be intimately triturated with sugar of milk, and then made into a pill-mass with suitable excipients.

3. **Pills liable to crumble** will keep their shape for a reasonable time if some fibrous materials, such as liquorice powder, paper pulp or lycopodium are added to the mass. If the pill-mass is too soft, it should be hardened on a hot plate, but if the ingredients are hard and brittle, they should be massed in a warm mortar. When the pill-mass contains dry vegetable powders some minutes must be allowed for the absorption of moisture before rolling.

4. **The same spatula** should never be dipped into the extract pot after it has been used to scrape the pill-mass from the tile, pestle and mortar.

5. **To prevent sticking together**, cinnamon or liquorice powder, mixture of starches, powdered French chalk are used. Pills containing hygroscopic and volatile ingredients should be varnished or coated and then dispensed in a well-stoppered or corked bottle. Pills for silvering should never contain glycerin.

6. **Substances that are decomposed by iron**, such as silver nitrate, copper, and bismuth salts, corrosive sublimate, and calomel, ought not to be mixed in an iron mortar, or scraped by an iron spatula.

7. **Crystalline salts** soluble in water should be very finely powdered, and massed with glycerin of tragacanth and some inert powder. Before silvering, they must be varnished with tolu and dried. Glycerin of tragacanth is the best excipient for insoluble salts.

8. **Essential oils.**—Soap and sometimes soap and powdered liquorice root make a good excipient. Wax is to be avoided. When there is much essential oil, the addition of liquor potassæ helps greatly.

9. **Potent Drugs.**—*To diffuse* potent drugs as atropine or strychnine, add a minute quantity of glycerin before massing.

10. **Scale preparations** should be finely powdered with a palette-knife instead of triturating in a mortar before massing. Use lanolin and kaolin, or mass rapidly with rectified spirit.

EXCIPIENTS

An excipient is a substance, either solid or liquid, added to bind the ingredients of a pill-mass into a plastic and adhesive mass. If none of the ingredients in the pill are suitable for producing a pill-mass, then it is necessary to add an excipient. The selection of a suitable excipient in these circumstances is done by the dispenser, which however requires experience. The following excipients are commonly used:—

1. **Acacia** in powder is a good excipient when judiciously used. It however makes the pill hard. With calomel it makes a regular cement. Combined with equal quantity of tragacanth it is better than acacia alone, and is known as Pulvis Acaciæ Co. It is frequently combined with syrup of glucose. It should not be used with wax, fats or oils, or with creosote.

2. **Alcohol** softens resinous substances, but the mass should be quickly rolled, otherwise it will crumble.

3. **Calcium Phosphate** in minute quantities gives a pilular consistence to greasy substances and essential oils when soap is not admissible. It is a good desiccant.

4. **Castor oil**, with or without soap, is a good excipient for making camphor pills.

5. **Compound decoction of aloes** is a good excipient for pills containing aloes. It should not be used when the pills contain any substance which is incompatible with carbonate of potassium.

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6. **Extract of gentian** though commonly used is not particularly adhesive and is dark in colour.

7. **Glycerin** keeps pills soft, but it is very hygroscopic. The addition of one-third of its weight of water overcomes its hygroscopic property. It is useful for pills liable to become hard.

8. **Glycerin, mucilage of acacia, water** and **alcohol** in equal parts make a good general excipient.

9. **Glucanth** consists of powdered tragacanth 1, glycerin 3, water 1, syrup of glucose 1. It is useful where glycerin of tragacanth is unsuitable on account of the large quantity of glycerin.

10. **Syrup of liquid glucose** contains liquid glucose 1, syrup 2, is a serviceable excipient.

11. **Kaolin ointment** is useful for massing oxidisable and reducible ingredients; but has no advantage over lanolin with which it may be combined.

12. **Lanolin** may be used in massing certain scale preparations. Being non-oxidisable it may be used to mass potassium permanganate or silver nitrate with prepared kaolin.

13. **Liquorice or marshmallow** in powder are absorbent and give elasticity to the soft mass. They are useful for pills containing oils or phenol.

14. **Proctor's paste** consists of powder tragacanth 1 dr., glycerin 3 drs., and water 1½ drs. The paste improves by keeping. It is an all-round good excipient.

15. **Resin ointment** is used for scale preparations, but wool fat is better.

16. **Soap powder** is the best excipient for vegetable powders, extracts and gum resins. It neither hardens nor crumbles. It should not be used for masses containing acids, acid salts, metallic salts, and substances containing tannin.

17. **Tragacanth** powder gives in small quantities solidity and elasticity to a soft mass; more so when the compound powder is used.

18. **Water** should be used with caution. It is a good excipient for masses containing gum or soap and makes a good pill with powdered opium.

19. **Wax** is not much used now for it makes pills indigestible, though it makes a beautiful pill-mass with camphor, creosote, phenol, and most of the essential oils.

Ince's Precautions.—The excipients to be avoided are :—

(*a*) Those incompatible with any of the ingredients of the pill-mass. Thus, confection of roses must not be used to make iron pills; acetic extract of colchicum must not be stiffened with magnesia

(*b*) Those which make the pill either too hard or too soft.

(*c*) Those which unduly increase size.

PILLS OF SPECIAL DRUGS

1. **Aloes** is best made into pills with a minute quantity of compound decoction of aloes, which has a great solvent power, or with syrup of liquid glucose. **Aloin** is massed with glycerin of tragacanth.

2. **Antipyrin** makes a good pill with glycerin of tragacanth.

3. **Argenti Nitras and Argenti Oxidum.**—The former is triturated with kaolin and massed with paraffin ointment, the latter with kaolin ointment.

4. **Bismuth salts** are best made into pills with glycerin of tragacanth.

5. **Butyl-chloral Hydrate** makes a good pill-mass with equal parts of powdered acacia, tragacanth and syrup.

6. **Calcium Sulphide** should be triturated with lactose to increase its weight if necessary, and massed with powdered tragacanth and

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glycerin. They should be varnished to protect from decomposition from the air.

7. **Camphor** should be powdered first with a few drops of alcohol, and after the evaporation of the spirit, use compound powder of acacia and mass with syrup of glucose.

8. **Camphor Monobromata** should be triturated with Pulv. Tragacanth. Co. and massed with Proctor's paste.

9. **Carbromalum** is made into a pill with glycerin of tragacanth.

10. **Cinchophen** makes a pill with compound acacia powder, 2 p.c. of tartaric acid and syrup of liquid glucose.

11. **Chlorbutol** with acacia and syrup of glucose.

12. **Citrate of Iron and Quinine** can be made into a pill by the addition of rectified spirit and rolling the mass quickly, or use kaolin and lanolin.

13. **Codeine** can be massed with half its weight of powdered liquorice and glycerin of tragacanth.

14. **Copaiba**, when massed with carbonate of magnesia, makes a very hard pill which is insoluble in the intestinal secretions. If it be made into an emulsion with gum, and be set aside for twelve hours, after adding 1 part of magnesia levis to every 10 parts of the balsam, it may be converted into a good pill-mass by the addition of a minute quantity of borax, and such a pill is soluble. Phosphate of calcium also makes a good pill.

15. **Creosote** with powdered curd soap gr. 1 and powdered liquorice gr. 2 for each minim makes a good mass. **Guaiacol** should be treated like creosote.

16. **Emetine and Bismuth Iodide** pill is made with acacia and tragacanth. The pills should be keratin coated or salol varnished.

17. **Ferri Sulphas.**—The granular sulphate forms a good pill with glycerin of tragacanth and a little powdered sugar of milk. **Ferri-sulphas exsiccat.** does not make a good pill. It cakes after a while. However, the following method may be tried :—The iron salt is to be triturated with equal parts of powdered acacia and tragacanth and massed with a mixture of glycerin 1 and water 2.

18. **Ferrum Redactum.**—First make a fine powder, add liquorice and mass with glycerin of tragacanth.

19. **Gallic Acid and Tannic Acid** make good pill-mass with glycerin of tragacanth.

20. **Hydrargyrum c. Creta** can be massed with glycerin of tragacanth. It should never be vigorously triturated in a mortar, as the mercury may separate.

21. **Hydrargyri Perchloridum** should be finely triturated with lactose and made into a pill with compound powder of acacia and syrup of liquid glucose. Calomel pills are also made in the same way.

22. **Ichthammol** is first mixed with tragacanth and then massed with liquorice.

23. **Menthol** should be worked like phenol. If it liquefies during manipulation, add calcium phosphate.

24. **Pepsin** can be massed with a mixture of equal parts of glycerin, syrup and water by quick rolling.

25. **Phenol** is first mixed with 2 grs. of liquorice for each grain, then triturated vigorously and rolled into pill quickly. A drop of mucilage of acacia may be necessary.

26. **Phosphorus** can be made into pills by the following method :—Phosphorus is dissolved in carbon disulphide and the solution is carefully mixed with oil of theobroma and beeswax, and made into a pill-mass with the addition of a little kaolin. The mass must be kept immersed in cold water in a blue bottle away from light. 3 grs. of the mass and 1 gr. of acacia powder can be rolled into a pill for dispensing.

Pills containing phosphorus require varnishing or a pearl coating.

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27. **Potassium Permanganate** requires careful treatment, for it soon oxidises when brought in contact with organic matter, such as sugar, syrup, vegetable extracts, etc. It can be made into a good pill-mass by mixing it with kaolin 50 p.c. and then making the pill-mass with hydrous wool fat. Work the mass gently. Vigorous rubbing or the introduction of even a trace of foreign matter may set up combustion.

28. **Quinine Sulphate** with tartaric or citric acid makes an excellent mass. Sometimes a drop or two of glycerin or water may be necessary in dry weather. The pills must be varnished or capsuled, otherwise, they will become soft and sticky by damp. Glycerin of tragacanth, is also a good excipient. White excipients should be used for white drugs.

29. **Rhubarb powder** is a troublesome substance for pill-making. Proof spirit or tincture of rhubarb (1 m. to 3 grs.) makes a soft mass which should be rolled quickly. Simple syrup, treacle and equal parts of glycerin and rectified spirit may also be used.

30. **Zinc Valerianate** makes a good mass with a little powdered acacia and spirit. Glycerin of tragacanth and liquorice powder may answer well.

PILL-COATING

Coating of pills is necessary to make them look more elegant, to disguise their unpleasant taste, to protect them from decomposition by contact with the air, and sometimes to prevent their action in the stomach.

1. **The general rule** in the coating of pills is that *all pills requiring a coating should be perfectly made, of a firm consistence, and free from contamination and powder.*

2. **Silvering** is done in a covered earthenware pot or a boxwood pill-silverer. The pills being damped with thin mucilage are dropped on to a silver leaf put within the silverer. The cover is then put on and the silverer is shaken for about a minute. After the superfluous fragments of silver-leaf have been blown off, the pills are exposed to air for a few minutes to dry. One silver leaf covers six 5-gr. pills, and two drops of mucilage are enough to damp a dozen of such pills. When the pills are too damp, more leaf is required for silvering, moreover the finish is not so elegant. A better and finer silvering can be obtained by putting the pills and leaf in a covered porcelain pot or a metallic silverer, heating the pot or silverer over a spirit lamp and rotating it as before.

Pills containing asafetida and sulphides should not be silvered unless they are very *stiff* and *varnished*, otherwise the silvering will soon get blackened. Pills containing mercury produce an unsightly amalgam.

3. **Gelatin-coating.**—A coating solution is made by dissolving 1 of gelatin in 4 of water on a water-bath, straining while hot, and cooling it afterwards. If there are air bubbles the solution should be repeated. The pills are now stuck on the points of pins or needles and dipped into the warm solution. The pills are taken out slowly and rotated for a few seconds and then stuck into a sheet of cork or pincushion by their opposite ends. As soon as the outside coating dries, the needles are withdrawn, and the holes close of themselves.

4. **Sugar-coating** is rather a complicated process. Dr. Symes recommends the following as the most practical method:—"Pills well dried on the surface are placed in a tinned copper bowl with a flat bottom, or an enamelled iron dish, the surface of which has been moistened with syrup, or syrup and gum. They are then rotated and gently heated, very finely powdered sugar being dusted on, and the motion kept up till a perfectly dry, hard and whitish coating is obtained, the operation being repeated if necessary."

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5. **Keratin-coating.**—Keratin solution is made by first removing from horn shavings all that is soluble in pepsin and diluted hydrochloric acid, dissolving the residue in alcoholic solution of ammonia or acetic acid, and then evaporating the solution to the consistence of a liquid gum. The pills are simply rotated with this solution in a pot and dried on a slab. The coating often gets sticky. Pepsinised keratin can be bought and dissolved in any of the above solvents. Drugs intended to pass undissolved through the stomach are coated with keratin or salol ; as emetine.

6. **Salol-varnishing.**—The varnish contains salol 2, shellac 3, absolute alcohol and ether of each 3, which should be applied several times till a thick coating is obtained. Or salol can be melted by heat in a copper bowl and the pills rotated as in sugar-coating.

7. **Enteric-coatings** are employed when pills are intended to pass through the stomach unchanged so that they can act in the intestine. The gelatin-coated pills are dipped in formaldehyde solution B.P., and dried. Many so-called enteric-coated pills are useless. These coatings are known as "glutoid" coating.

POWDERS

1. **Compound Powders.**—The B.P. gives no directions as to the manner of mixing compound powders, consequently the dispenser is left to his own experience and resources in compounding them. The following hints, however, will greatly help him.

(*a*) **Powders must be thoroughly mixed** in a mortar or on paper. Powders mixed by a spatula on paper and sifted are more diffusible in water than those rubbed up in a mortar ; but there are exceptions to this rule. Take for example the following prescription :—℞ Sulph. Precipit. gr. 20, Guaiaci Resin gr. 10, Magnesia gr. 20. Here the most miscible powder is obtained by triturating guaiacum and magnesia together in a mortar, before adding sulphur, whereas if mixed on paper, it would not diffuse in water. Powders for insufflation should only be loosely mixed on paper.

(*b*) They should be **passed and repassed through a fine hair sieve** as often as possible. By repeated sifting and shaking in a bottle the ingredients are thoroughly incorporated and a uniformity of colour is obtained.

(*c*) They should be **very lightly rubbed** in a mortar if this process is at all adopted, otherwise they would cake.

(*d*) **Ingredients in smaller quantities** should first be thoroughly mixed together, and afterwards larger quantities be gradually incorporated.

2. **Folding Paper and Boxes.**—Powders should be folded in ordinary writing paper, or better if possible, in demy glazed powder-paper made for the purpose. Waxed or paraffined paper is to be used for hygroscopic drugs. Coloured paper is used for powders for lotions. Folded powders should be of the same breadth and length, better done on a powder-folder. Powders under six are generally dispensed in a neat small oblong envelope on which "The Powder" is printed ; but those over six in a cardboard box or bottle with a label gummed outside.

3. **Waxed Paper and Tinfoil.**—Drugs that are **perishable**, as ergot ; that are **volatile**, as camphor, essential oils ; that are **hygroscopic**, as potassium acetate, carbonate and citrate, and sodium iodide, etc. ; that are liable to **decomposition**, as calcium sulphide, valerianates, should be folded first in waxed paper and then each covered with tinfoil and dispensed in a bottle.

4. **Powders in Quantity.**—When a powder is ordered to be given in spoonfuls, it should be dispensed in a well-corked or stoppered, wide-mouthed bottle.

5. **Salts** which mutually decompose each other must be mixed

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and stirred lightly together in a dry condition; as sodium sulphate with potassium tartrate, potassium nitrate with sodium salicylate.

6. **Oxidising Substances** should be each separately rubbed to powder, and then lightly blended on paper with safe ingredients by a bone spatula.

7. **Hygroscopic Powdered Drugs** should never be kept in paper packets. They should be dried and preserved in wide-mouthed bottles or stone jars with accurately fitted stoppers or corks. Suspending a bag of dry quicklime from the cork helps also to keep powders dry. Powdered squill and ammoniacum can be kept dry in this way.

8. **Division of Powders.**—There should be no guesswork in division. **Each one must be weighed.**

9. **Liquids** are rarely prescribed in powders; if so, white kieselguhr may be used to absorb them (1 gr. to 1 m.).

BLISTERS

1. **Blister Spreading.**—A blister is best spread over an adhesive plaster, which has been previously spread upon glazed thin calico. First of all the dispenser should cut a "shape"—an exact size and form of the blister ordered—out of a square piece of writing or packing paper, leaving all round a margin 1 inch wide. This is best done by folding the square piece twice upon itself, and cutting by a pair of scissors the shape of the blister out of the middle, rejecting the cut out central piece. This *empty space is the shape of the blister.* The dispenser now cuts a piece of spread adhesive plaster or adhesive plaster mull one inch bigger than the size ordered, and gently warms it to make it slightly sticky, and quickly lays the "shape" upon its sticky surface, and evenly presses it down. (In India the warming of the adhesive plaster is not often necessary during hot months). He then takes a quantity of the B.P. cantharidin plaster sufficient for the size and softens it well between his thumb and fingers. Taking a small pellet, he spreads over the adhesive surface, with the side and front of his right thumb, while the fingers of his left hand keeps the plaster *in situ.* He goes on making a series or rainbow-like strokes from left to right till the whole of the surface within the shape is covered. A long spatula, not unlike a large dinner knife, is gently warmed, and firmly passed over the spread cantharidin, removing any superfluous plaster and making its surface smooth. The paper shape is now removed, and the edges are neatly trimmed, keeping a margin of the plaster three-eighths of an inch wide. A piece of oiled or waxed paper is now loosely laid over the blister and the whole put within a paper box.

2. **Powdered Cantharides, Blistering Liquid** or **Olive Oil** should not be sprinkled or applied to increase the action, or improve the appearance, of the blister.

3. **Paper-Covering** should be removed before use, otherwise the blister will not stick. Both the dispenser and prescriber should give directions to this effect. A better plan is to pin the margins to a piece of paper which is then stuck to the bottom of the box.

PLASTERS

Most of the plaster-mulls of the market are made by machinery. Dispensing of such a spread plaster means the cutting of a piece ordered. It is only when a special plaster is ordered that the dispenser is required to make one on the counter. The spreading of a plaster requires great skill and dexterity.

1. **Plaster spreading.**—A plaster is made in the same manner as a blister, except that the method of spreading is different. Sheepskin, stiff chamois, dimity, moleskin or sometimes adhesive plaster-mull

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is used, but the white sheepskin is generally preferred when not otherwise ordered by the prescriber. The "shape" is cut in the same way as for a blister. A piece of leather larger than the size of the plaster ordered, is cut off and stretched out in all directions by pulling. The leather is now placed with its rough surface upwards on a thick pad of paper, and the gently warmed plaster iron is passed over it, to remove any wrinkles or inequalities. The paper shape merely dipped in water is evenly pressed against this rough surface, and all the necessary appliances being in readiness the process of spreading is begun, in one or other of the following ways :—

(*a*) The plaster is cut into thin slices, put in a small enamelled pan with a lip and handle, and warmed over a gas flame or fire, stirring it constantly and not allowing it to boil. In the meantime the leather, the shape, and the plaster iron or spatula are kept ready as already described. As soon as the plaster becomes creamy, it is poured over the leather within the shape at the left end, then with a long spatula or a plaster iron it is spread rapidly over the surface, any superfluous plaster being removed and returned to the pot.

(*b*) The easiest and most convenient method of spreading is to cut a piece of plaster from the stick, allowing 15 grs. for each square inch of plaster required, and to put it on a sheet of strong, smooth, brown paper. Having prepared the shape and the leather, melt the cut-off piece to a creamy consistence by gently rubbing a hot plaster iron over it, and scrape the mass to the edge of the paper. The leather with the shape, having been brought alongside with one or two sweeps the dispenser covers the whole surface, removing any superfluous plaster with a spatula. A second hot iron may be required at this stage.

A mixture of plasters can be made by a similar process.

2. **Plaster with an adhesive margin** is made in the following manner :—The shape is cut as before, and the central piece instead of being thrown away, is damped and stuck to the middle of the leather. The shape is again folded up, and a piece of the width of the intended adhesive margin is cut off ; and the shape is pressed against the leather, thus leaving a free space between the centre-piece and the shape ; which space is now covered over with the adhesive plaster. When cold, remove both the papers and apply a second shape cut to the proper size, having previously coated it lightly with soft soap to prevent it from sticking to the adhesive margin. The plaster is now spread in the ordinary way, the shape removed, and any soap that may have adhered to the margin is wiped away with a wet cloth or sponge.

The Writer's Method.—The plaster is spread as usual and the shape is pulled off, and the margin of the leather trimmed, leaving exactly the width to be covered over with the adhesive plaster. The dispenser now melts a small piece of adhesive plaster in a gallipot, and with a spatula spreads it over the margin and finally smooths it by passing a hot spatula over.

3. **Plasters for bed-sores** are spread on chamois leather without margins.

4. **Mammary plasters** must be circular in shape, 7-in. in diameter, with an opening 2-in. in diameter in the centre. The margin is to be notched to fit these plasters to the curved surface of the breasts.

SUPPOSITORIES, PESSARIES AND BOUGIES

1. **Basis.**—Oil of theobroma is the official basis. It should be liquefied on a water-bath in a casserole or a porcelain evaporating dish. In India and the Colonies, where the prevailing temperatures are higher than in England, a sufficiency of white beeswax may be added to raise the melting-point to the necessary degree. An

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alternative method is to use *glyco-gelatin basis*, which consists of gelatin 25; glycerin 40 (by wt.); and water 80 (by wt.). This should only be used when ordered, since gelatin is incompatible with several substances including tannin.

2. **Ingredients** should be treated like those for ointments. Any powder or crystalline substance must be rubbed very fine with a little cacao butter, before mixing with the melted oil of theobroma.

3. **Moulds** are necessary to make suppositories. They are made of heavy gun-metal with six to twelve holes into which the melted suppository mass is poured. The mould is divided longitudinally so that it can be opened and cleaned. Each half of the mould contains the corresponding hollows, which when fixed and screwed form the entire suppository holes. They are so made that each hole has the capacity of holding 15 gr. or 30 gr. suppository.

Moulds must be perfectly clean and cooled with ice or cold water and the inner surface of the hollows lubricated with a piece of cotton wool soaked in soap liniment and glycerin, equal parts, or with soap liniment 3 parts and almond oil 1 part. Almond oil is necessary for gelatin suppositories.

4. **Operation.**—Triturate as in para 2, and mix with the melted oil of theobroma with constant stirring, until a creamy mass without lumps is obtained, and then pour it into the moulds, or divide into equal parts when hard, and mould them with the fingers into the shapes of suppositories, pessaries and bougies. Finely powdered starch prevents them from sticking during manipulation.

SUPPOSITORIES AND BOUGIES OF SPECIAL DRUGS

1. **Adrenaline** should be dissolved in about 10 minims of 1 in 30 boric acid solution and then mixed with suppository basis which consists of a mixture of oil of theobroma and sodium stearate ½ gr. for each suppository ordered. Stir till an emulsion is formed and pour into the mould when about to set.

2. **Alkaloids.**—Alkaloidal salts are generally better absorbed than pure alkaloids, and therefore the salts instead of the alkaloids should be used dissolved in oleic acid.

3. **Boric Acid** makes a good mass if glycerinum acidi borici and gelatin basis are mixed together.

4. **Chloral Hydrate** should not be mixed with heated cacao butter, but rubbed up with cold cacao butter and a little wax, if necessary, and pressed into the mould.

5. **Extracts** must be made into a smooth paste with water or proof spirit, and gradually mixed with the melted basis.

6. **Ichthammol** suppositories are made with glyco-gelatin basis when each suppository is more than 2 grs., otherwise oil of theobroma may be used. The ichthammol should be added directly to the melted oil of theobroma.

7. **Iodoform** makes good bougies and suppositories with cacao butter by the cold process. The crystals must be finely powdered in a glass mortar before being incorporated in the oil.

8. **Despatching.**—These preparations should be sent out wrapped in absorbent cotton-wool. In hot weather, they may be dispensed in a wide mouth stoppered bottle containing iced water. If they contain volatile ingredients, each of them should be covered with waxed paper or tinfoil.

TINCTURES

In the preparation of tinctures three things are essential, *viz.*—(1) the **Solvent**; (2) the **Process**; and (3) the **Ingredients.**

1. **Solvent.**—Alcohol of various strengths is used in the preparation of most tinctures. One only, *viz.* Tr. Lobeliæ Ætherea is prepared with ether. Ammo-

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nia is used in the preparation of tr. valerianæ ammoniata. Glycerin and distilled water are used to help solution of active ingredients.

2. **Process**.—Any of the following processes is used for making tinctures.

(*a*) *Maceration*.—Place the solid materials with the whole of the menstruum in a closed vessel; shake occasionally during seven days; strain; press the marc, mix the strained and expressed fluids; filter. It takes seven days and is not economical.

(*b*) *Percolation*.—Moisten the solid materials with sufficient menstruum, set aside for 4 hours in a well-closed vessel; pack in a percolator, add sufficient menstruum to saturate the material. When the liquid drips from the percolator close the outlet, add sufficient menstruum to leave a layer above the drug. Macerate for 24 hours. Allow to proceed till the percolate measures about three-fourths of the volume required for the finished tincture. Press the marc, mix the expressed liquid with the percolate, add sufficient menstruum to produce the required volume, filter.

(c) *Simple Solution*.—This method is adopted when tinctures are made by dilution of a liquid extract or a stronger tincture.

3. **Ingredients**.—These require to be carefully selected. Most of them are to be *powdered* according to the degree of comminution as prescribed by the B.P. Some are to be *cut small*, some to be *bruised*, and some are used in their natural state.

LOZENGES

1. **The B.P. lozenges** are made like a pill-mass (*see* page 35).

2. **Ingredients**.—The essential ingredients for making lozenges are finely powdered or icing sugar, mucilage of picked gum acacia, and medicinal and flavouring agents.

3. **Operation**.—The ingredients having been thoroughly mixed and kneaded, the resulting paste is placed on a slab with adjustable edges and rolled out to the desired thickness. The lozenges are then cut out with a punch and exposed to the air for 12 or 24 hours, after which they are removed to a drying chamber.

4. **Stamping**.—While the lozenges are still soft, they are stamped with letters indicative of their composition.

5. **Packing**.—Lozenges should be kept in dry, well-fitted stoppered bottles in a dry place. Dampness makes them sticky. They are to be dispensed in wide-mouthed stoppered bottles.

OINTMENTS

1. **The preparation of ointments** is not always easy. Special tact and care can only turn out a good product. The following general hints are worth remembering :—

(*a*) If the active drug is a *solid* or a *powder*, as galls, mercuric iodide, sulphur, etc., it should be reduced to a state of fine powder before admixture with the basis, so that the ointment may be free from grittiness.

(*b*) If it is a *soluble* or *deliquescent salt*, as potassium carbonate or iodide, it should be first made into a thin paste with water before mixing with the basis.

(*c*) If it is a *hard extract*, a *balsam*, or a *resin*, a preliminary treatment is necessary with such substances as water, oil, glycerin, or rectified spirit, as the case may be.

(*d*) If it is a *liquid extract*, as in the case of belladonna ointment, it must be evaporated to the required consistence.

(*e*) If it is an *alkaloid*, as aconitine, atropine or cocaine, it should be dissolved in oleic acid by trituration and gentle heat.

(*f*) If it is a *crystallised drug*, as boric acid, salicylic acid, iodoform, etc., it should be reduced to a fine powder, and triturated with its own weight of the basis for a while before adding the rest. Tannic acid should first be dissolved in glycerin.

(*g*) If it is a *volatile substance*, such as menthol, chloral hydrate,

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hydrocyanic acid dilute, it should be mixed after all the ingredients have been incorporated so as to reduce its evaporation to a minimum.

2. **Basis.**—Ointment bases are of two kinds, (1) *those used when the active ingredients are intended for absorption from the skin*, and (2) *those used when the medicaments are intended for local action only.* For the former class of ointment lard or benzoinated lard, or suet or benzoinated suet are used. For the latter class soft or hard paraffin or both with or without beeswax are used. In both cases wool fat may be added if a large quantity of liquid is to be incorporated.

Whatever basis is selected it should not be a chemical incompatible, nor should it in any way affect the action of the ointment. Rancid lard or ointment should not be used. If the basis becomes too soft on account of the prevailing high temperatures, as in India and the Colonies, benzoinated lard, lard, suet, or beeswax may be added as required.

When the basis contains substances like hard paraffin, beeswax, lead plaster or such ingredients which are solid at the ordinary temperature, and have to be incorporated with soft paraffin, lard, suet or an oily substance, it is necessary that they should be prepared by fusion, *i.e.*, by melting them in a porcelain dish on a water bath. The substances with a high melting point should be shredded and melted first and the other ingredients of the base added according to their melting point.

3. **Incorporation of a liquid** with a fatty or oily basis is best effected by slowly adding the liquid drop by drop, and keeping up a steady rotatory motion. The mortar must be warmed beforehand.

4. **Spatulas.**—A bone or boxwood spatula is the best for scraping, stirring or mixing ointments.

5. **Two ointments**, or an ointment and a liquid or oily substance, are best mixed on a porcelain slab.

6. **Oleates** should not be melted in a metallic cup, but in a porcelain casserole.

7. **Tinctures and spirituous substances** are best incorporated with a fatty medium by spreading the latter evenly on the bottom and side of a mortar, and mixing the tinctures gradually.

OINTMENTS OF SPECIAL DRUGS

1. **Unguentum Phenolis, B.P.** is best prepared by using liquefied phenol and a cold basis, as previously prepared part of the phenol crystallises on keeping. This is obviated by dissolving the phenol in glycerin.

2. **Chrysarobinum, B.P.** when dissolved by heat partly recrystallises on cooling, as happens in the B. P. ointment. It being more soluble in castor oil than lard, a mixture of the two gives satisfactory results.

3. **Glycerin** can be well incorporated with extracts by first rubbing the extract with a little hot water in a warm mortar and then adding glycerin gradually.

4. **Hydrargyri Perchloridum** is sometimes prescribed in the shape of ointment. It must be well triturated with glycerin (2 ms. to 1 gr.) before mixing with basis, otherwise minute particles of it may violently irritate the skin. When ordered with potassium iodide, each should be triturated first before admixture.

5. **Iodide.**—First triturate, then add a few drops of rectified spirit and rub with its own weight of fatty basis, and lastly mix with the remaining basis.

6. **Paraffin ointment, B.P.**—Unless the melted paraffins are stirred well, the ointment is sure to be lumpy. White soft paraffin should be used for colourless ointments.

7. **Resorcin** readily absorbs oxygen and becomes discoloured.

8. **Thymol crystals** are very irritaing to the skin. With camphor

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(1 to 1), thymol forms a liquid which can be worked up into an ointment.

9. **Despatching.**—Ointments should be sent out in earthenware pots with celluloid caps, a piece of waxed paper intervening between the cover and the ointment. They may also be sent out in glass jars having glass or aluminium covers. Collapsible tubes are convenient for small quantities and when the ointment is made by fusion. When open pots are used a tinfoil should be used over the waxed paper.

10. **Eye ointments** or **oculenta** must be prepared under aseptic conditions according to the directions given in the B.P. Suitable glass rods for the application of the ointment should be supplied and their use explained to the patient.

STERILISATION

The use of different preparations which are introduced into the body through different channels and of other preparations like the different ointments for the eye, demands that these should be sterile, *i.e.*, free from living micro-organisms. A knowledge of the different methods of sterilisation is therefore necessary. The methods generally adopted for the purpose involve either application of heat (moist or dry), filtration, use of certain chemicals, or a combination of these. Whatever method may be adopted it must be such as will not inactivate the medicament, or render the preparation subjected to the process, unsuitable for the purpose for which it is specially intended.

Since heat kills most bacteria, sterilisation by heat is generally the most suitable and convenient method. It is therefore the method of choice for thermostable substances, while filtration is adopted for thermolabile substances. Certain chemicals have a marked disinfectant action and kill most bacteria. Their relative value has already been discussed (*see* page 520), but it is necessary to mention that some of these substances are used as a preservative in sterile solution as a precaution against possible reinfection. The chemicals generally used are phenol, cresol and chlorbutol. Sodium chloride increases the potency of phenol and cresol as antiseptic.

The Pharmacopœia sanctions the following methods for sterilisation:—

1. *Heating in an Autoclave.*—Glass vessels and containers, and various solutions or suspensions for injection should be sterilised in an autoclave. Glass containers require a heating for one hour at 150° C. When the volume of each container does not exceed 100 mils, the containers are exposed to steam at 115° to 116° for thirty minutes, and this temperature is reached when the pressure of the steam is 10 lbs. per square inch above the atmospheric pressure. When the containers contain more than 100 mils of fluid, they are exposed for a longer period, sufficient to ensure that the whole of the solution in each container is maintained at the temperature of 115° to 116° for thirty minutes.

2. *Tyndallisation.*—By this is meant intermittent heating at temperatures between 60° to 80° for three successive days for materials which are not immediately wanted for use and which will not be injured by a temperature of 80°. The principle underlying this method is that most bacteria are killed during the first heating but not the spores, so they are exposed for three successive days to allow the spores to germinate and thus make them susceptible to the action of subsequent heat.

3. *Filtration.*—This consists in passing the material to be sterilised through sterile bacteria-proof filter (Berkefeld or Chamberland). The filter should be first sterilised by heating in an autoclave at 115° to 116° for thirty minutes, or in a steam steriliser for one hour on three

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successive days. All substances sterilised by this process must comply with sterility tests prescribed by the B. P. before being used. This method is applied to those substances which would be inactivated by heat.

4. *Emergency Method.*—The solution is first prepared by aseptic methods and an antiseptic is added in such concentration as will prevent the growth of bacteria at least as effectively as 0.5 p.c. *phenol.* The solution is distributed into previously sterilised containers and sealed. These are heated by immersion in water or by other means so as to maintain the temperature of the solution at 80° for not less than 30 minutes. The containers are labelled giving the date and the warning "keep in a cool place and use within four days". In solutions intended for intravenous injection the addition of the anitseptic is omitted; and the solution is prepared by aseptic methods, and then boiled for fifteen minutes.

5. *Sterilisation of Oily Solutions.*—This should be sterilised by heating to 150° for one hour. When this cannot be done without producing physical or chemical change, the solution or suspension is prepared by aseptic methods, and oil, which has been heated to 150° for one hour is used. This is then transferred to previously sterilised containers and these are sealed to exclude bacteria.

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APPENDIX I

EXTRACT FROM THE RULES FOR REGULATING THE POSSESSION FOR SALE AND THE SALE OF POISONS

Under Indian Poisons Act, 1919 (xii of 1919)

* * * *

15. The following restrictions shall apply to "whole-sale" of poisons: –

(*a*) All receptacles containing poisons shall be securely packed and bear the label "Poison," the name of the poison and, at the time of sale, the name and address of the seller as well, except where the manufacturer's name appears thereon.

(*b*) In case of sale of poisons included in Schedule I, a stock and sale register in the form appended to these rules, shall be maintained in which all transactions shall be entered from day to day in the manner indicated therein, provided that no signatures of purchasers shall be necessary and sales may be posted in lots of all poisons sold under a particular order according to the serial numbers of the transactions. All letters or written orders referred to in the fifth column of sale registers shall be preserved in original, where possible, for 2 years from the date of sale.

16. The following restrictions shall apply to "retail sale" of poisons included in Schedule I:—

(*a*) Every vessel, package or covering containing poisons shall be labelled with the name of the poison, and the word "Poison" and in case of preparations for external use only the words "not to be taken" in addition, distinctly printed both in English and vernacular, in red letters.

Note.—In exceptional cases when printed labels are not immediately available, written labels may be used. If labels are written, only block capitals and red ink shall be used.

(*b*) All poisons which are kept for sale by the licence-holder under these rules shall be kept in a box, almirah, room or building (according to the quantity maintained) secured by lock and key, and in which no substance shall be kept other than poisons possessed in accordance with a licence granted under the Act, and each of these poisons shall be kept in a separate closed receptacle within such box, almirah, room or building. Every such box, almirah, room or building and every such receptacle shall be marked with the word "Poison," in red characters both in English and vernacular and in the case of receptacles kept for separate poisons, with the names of such poisons.

(*c*) When any poison is sold it shall be securely packed in a closed receptacle or packet which shall be labelled by the vendor with a red label bearing the name of the poison and the word "Poison" and in case of preparations for external use only, the words "not to be taken" in addition, in English and vernacular, and the name and address of the vendor, together with the date of sale.

(*d*) Every sale of such poisons shall, so far as possible, be conducted by the licence-holder in person or where the licence-holder is a firm or company, through or under the supervision of an accredited representative of such firm or company or, in either case, through a qualified compounder.

(*e*) A licence-holder shall not sell any poison to any person unless he is personally known to him, or is identified to his satisfaction, or

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to any one who is apparently under 18 years of age, or to any one who does not appear to him to be in full possession of his faculties, or to any wandering mendicant.

(*f*) Every licence-holder shall maintain a stock register in the form appended to these rules in which he shall enter or cause to be entered the sales of poisons specified in Schedule I according to the instructions contained in the register. Separate pages shall be allotted in the register for each particular poison and the licence-holder shall enter or cause to be entered thereon, side by side, all stock and sales of poison. The register shall be totalled and balanced daily and the licensee shall be himself responsible for its correctness.

(*g*) The licensee shall completely fill in the prescribed sale register before delivery of such poisons.

(*h*) A licence-holder shall not sell powdered white arsenic unless the same is, before the sale thereof, mixed with soot, indigo, or Prussian blue in the proportion of at least ½ oz. soot, indigo or Prussian blue to 1 lb. of white arsenic and so on in proportion for any greater or less quantity; provided that where the licensing authority is satisfied that such arsenic is required for some purpose for which such admixture would, according to the representation of the vendor render it unfit, the said licensing authority may authorise the vendor in writing to sell without such admixture, such quantity of white arsenic as the licensing authority may think proper.

17. The following restrictions shall apply to the "sale of poisons" included in Schedule I "by dispensing of prescriptions":—

(*a*) The stock of poisons for dispensing purposes shall be kept in the dispensing room in a separate almirah or shelf and the room or the almirah shall be locked up after dispensing hours. Such poisons shall be kept in separate bottles or other receptacles distinguishable by touch and colour from ordinary bottles and receptacles and marked with the word "Poison" in English and the vernacular and the name of the poison in red letters in English.

(*b*) When a poison is sold without any mixture, all restrictions referred to in rule 16 (*c*), (*d*), and (*e*) regarding poisons sold and method of sale, shall apply.

(*c*) A stock register in the form appended to these rules shall be maintained and kept up to date but the consumption of poisons in the dispensing room need not be shown on the sale side of the register but a record of the prescriptions under which poisons are sold shall be preserved for 2 years.

18. Where the sale of poisons included in Schedule I is carried on both by retail and by prescriptions, poisons issued from stock to the dispensary on any day, shall be entered forthwith as one item on the issue side of the register with a note to that effect, provided that the stock so transferred shall not exceed a reasonable quantity. No detailed particulars are, however, required to be maintained in the said register regarding the consumption of such poisons in the dispensary for dispensing purposes.

19. All the restrictions mentioned in rule 16 (*a*), (*b*), (*c*), (*d*) and (*e*) shall apply to the possession for sale and sale of poisons enumerated in Schedule II.

* * * *

SCHEDULE OF POISONS

SCHEDULE I

1. Aconite, Aconitine, Lin. Aconite, Tinct. Aconite.
2. Arsenic metal, Arsenious Oxide (white arsenic), Yellow Arsenic (arsenic sulphite, yellow orpiment), Red Arsenic (Realgar), Copper Arsenite (Scheele's green), Copper aceto-arsenite (Paris green), Liqr. Arsenicalis, Liqr. Arsenic Hydrochloride, Arsenic chloride, Arsenic bromide.

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3. Atropine, Atropine Sulphate, Liqr. Atropin. Sulphate, and other salts and preparations of atropine.
4. Barium Sulphide.
5. Belladonna root, Belladonna leaves, Extracts and Liquid Extracts of Belladonna, Liniment Belladonna.
6. Cannabis Indica, Extract of Cannabis Indica.
7. Cocaine, Cocaine Hydrochloride, and other salts and derivatives of Cocaine, both synthetic and natural, except such as are exempted under the Excise Act.
8. Corrosive Sublimate (Mercuric Chloride).
9. Cyanide of Potassium, Cyanide of Sodium, Acid Hydrocyanic (prussic) concentrated and dilute.
10. Datura Folio, Datura Seeds (Strammonium).
11. Morphine, Morphine Hydrochloride, Liqr. Morphine Hydrochloride, Morphine Acetate, Liqr. Morphine Acetate, Heroin, Heroin Hydrochloride, and other salts and derivatives of morphine.
12. Nux Vomica Seeds, Extract of Nux Vomica Solid, Liquid Extract of Nux Vomica, Tinct. Nux Vomica.
13. Opium, Tinct. Opium, Extract of Opium Solid, Extract Opium Liquid, Liqr. Opii Sedativus.
14. Phosphorus yellow.
15. Picrotoxin.
16. Savin oil (oil sabinæ).
17. Strychnine, Strychnine Nitrate, Strychnine Sulphate, Strychnine Hydrochloride, Liqr. Strychnine Hydrochloride, and all other salts and solutions and preparations containing 0.2 per cent. or more of strychnine.
18. Tetra ethyl lead.

Schedule II

1. Antimony compounds, both organic and inorganic.
2. All organic compounds of Arsenic, and all other inorganic compounds of Arsenic except those mentioned in Schedule I.
3. Barium Nitrate, Barium Chloride,
4. Cantharides, Tinct. Cantharides, Cantharidin, Tinct. Cantharidin.
5. Carbolic acid containing not less than 3 per cent. of phenol.
6. Chloral hydrate.
7. Digitalis Folio, Tinct. Digitalis, Digitalin.
8. Hyoscyamus (Henbane or Khorasani Ajwan) leaves, Ext. Hyoscyamus Liquid Tinct. Hyoscyamus, Liq. Hyoscyamine Sulphate, Hyoscine Hydrobrom.
9. Mercury oxides (red, yellow or black), Ammoniated Mercury, Mercury Sulphocyanide, Mercury Iodide, Liqr. Hydrarg. Perchlor.
10. Nitric Acid, concentrated.
11. Oxalic acid, Sodium Oxalate, Potassium Oxalate, Ammonium Oxalate.
12. Red Phosphorus, Rat poison containing red phosphorus.
13. Strophanthus, Strophanthin, Ext. Strophanthus Liq., Tinct. Strophanthus.
14. Tinct. Belladonna.
15. Chloroform.

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Stock Register

NAME OF THE FIRM.....

ADDRESS.....

NAME OF THE POISON

Date of receipt.	Name and address of person or firm from whom received.	Quantity received.	Date of sale.	Amount sold.	Balance in stock.

Sale Register

NAME OF THE FIRM.....

ADDRESS.....

NAME OF THE POISON

Date of sale.	Name and address of purchaser.	Purpose for which wanted.	Quantity sold.	Signature of purchaser (or thumb-impression if illiterate) or in case of purchase by post, date of letter or written order and reference to the original in the file in which it is preserved.	Remarks.

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APPENDIX II

CONTRACTION OF WORDS AND PHRASES USED IN PRESCRIPTIONS

The following contractions of words are ordinarily seen in prescriptions :—

Contr.	*Name*	*Meaning*	*Contr.*	*Name*	*Meaning*
aa	Ana	Of each	M.	Misce	Mix
Ad.	Adde	Add	M. or Min.	Minimum	A Minim
Amplus	.....	Large	Mag.	Magnus	Large
Aq.	Aqua	Water	Mane	.....	In the morning
Aut	.....	Or			
C.	Cum	With	Mist.	Mistura	A mixture
Cap., Cpt.	Capiat	Let the patient take	Mitte	.....	Send
			Mol.	Mollis	Soft
Cibus	.....	Food	Nox	.....	Night
Colo	.....	To strain	Om.	Omnis	All, every
Co. or Comp	Compositus	Compound	Post	.....	After
Cras	.....	To-morrow	R.	Recipe	Take
Cum	.....	With	Rept.	Repetatur	Let it be repeated
Cyath.	Cyathus	A glass			
Div.	Divide	Divide	Sig.	Signa	Mark thou
Et	.....	And	Sine	.....	Without
F.	Fac	Make	Ss.	Semis	Half
Ft.	Fiat	Let it be made	Somnus	.....	Sleep
			Stat.	Statim	Immediately
Garg.	Gargarisma	A gargle	Sum.	Sume	Take
Gr.	Granum	A grain	Talis	.....	Such
Gtt.	Gutta	A drop	Una	.....	Together
Haust.	Haustus	A draught	Vel.	.....	Or
H.	Hora	An hour	Ver.	Verus	Genuine
In	.....	In or into	Vesp.	Vesper	The evening
Ind.	Indies	Daily.	Vetus	.....	Old
Levis	.....	Light	Vitellus	.....	The yolk of an egg
M.	Massa	A mass			

The following contractions of phrases are often used in prescriptions :—

Contraction	*Phrase*	*Meaning*
Ad lib.	Ad libitum	At pleasure.
A. H.	Alternis Horis	Every other hour.
A. C.	Ante cibus	Before food.
Aq. Bull.	Aqua Bulliens	Boiling water.
„ Dest.	„ Destillata	Distilled water.
„ Ferv.	„ Fervens	Hot water.
„ Font.	„ Fontalis	Spring water.
„ Pluv.	„ Pluvialis	Rain water.
Bis ind. or B.D.	Bis indies	Twice daily.
B. P. or Ph.B.	Pharmacopœia Britannica	British Pharmacopœia.
C.M.	Cras mane	To-morrow morning.
C.N.	Cras nocte	To-morrow night.
Coch. amp.	Cochleare amplum	A table-spoonful.
„ mag.	„ magnum	Do.
„ mod.	„ modicum	A dessert-spoonful.

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Coch. min. ...	... Cochleare minimum	... A small spoonful or a teaspoonful.
,, **parv.** ...	... ,, parvum	... A tea-spoonful.
C. Vinar. ...	... Cyathus Vinarius	... A wine-glass.
Dieb. alt. ...	... Diebus alternis	... On alternate days.
D. in p. æ or Div. in p. æq.	... Dividatur in partes æquales	... Let it be divided into equal parts.
F. A. O. ...	... Folio Argenti Obruantur	... Let it be rolled in silver leaf.
Ft. Haust. ...	... Fiat Haustus ...	... Let a draught be made.
F. M or Ft. Mist.	... Fiat Mistura ...	... Let a mixture be made.
Ft. Mas. in pil. xii div.	... Fiat Mass in pilulæ xii divide ..	... Let a pill mass be made and divide into 12 pills.
H. D. ...	... Hora decubitus ...	.. At bedtime.
H. S. or H. S. S.	... Hora Somni Sumendum	... To be taken at bed time.
M. B. ...	... Misce Bene	... Mix well.
M. D. U. ...	... More dicto utendum.	... To be used as directed.
M. P. ..	... Massa Pilularis ...	... A pill mass.
Mic. pan. ...	... Mica panis ...	... Crumb of bread.
O. H. ...	... Omni Hora ...	... Every hour.
O. M. ...	.. Omni mane ...	.. Every morning.
Omn. bih. ...	.. Omni bihora ...	.. Every two hours.
O. N. ...	.. Omni nocte ...	.. Every night.
P. C. ...	... Post Cibus ...	... After food.
P. P. A. ...	... Phiala prius agitata	... The bottle to be first shaken.
P. R. N. ...	... Pro re nata ...	... When required, occasionally.
Q. s. ...	... Quantum sufficiat ...	... Sufficient quantity.
Q. h. ...	... Quaque hora ...	... Each hour.
S. O. S. ...	... Si opus sit ..	... If necessary.
S. S. ...	... Statim sumendum...	... Immediately to be taken.
T. d. ..	... Ter in die ...	... Thrice daily.

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APPENDIX III

ALTERNATIVE PREPARATIONS SANCTIONED FOR USE IN TROPICAL, SUBTROPICAL, AND OTHER PARTS OF THE BRITISH EMPIRE

Aurantii Cortex.—In parts of the Empire where bitter oranges cannot be obtained, either dried bitter-orange peel or fresh sweet orange peel may be used in preparing tincture of orange.

Emplastra.—Varying quantities of hard soap, colophony, or yellow beeswax, may be employed in the preparation of the plasters of the Pharmacopœia, when prevailing high temperatures otherwise render the basis too soft for convenient use ; but the official proportion of the active ingredient must be maintained.

Extracta Liquida.—Any Pharmacopœial liquid extract containing less than 30 p.c. v/v of ethyl alcohol, may have the proportion increased to an amount not exceeding 30 p.c. v/v, where otherwise the preparation will be liable to ferment.

Limonis Cortex Siccatus.—When fresh lemon peel cannnot be obtained, dried lemon peel may be used in preparing fresh and concentrated compound infusions of gentian, syrup of lemon, and tincture of lemon.

Oleum Olivæ.—In parts of the Empire where olive oil is not readily available, arachis oil or sesame oil, but no other oil or fat, may be employed in place of olive oil in making the official liniments plasters, ointments, and soaps for which it is directed to be used.

Unguenta.—Varying quantities of benzoinated lard, lard, suet, yellow beeswax, or white beeswax, may be employed in the preparation of the ointments of the Pharmacopœia when prevailing high temperatures otherwise render the basis too soft for convenient use ; but the official proportion of the active ingredient must in all cases be maintained.

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ADDENDUM 1936
TO THE BRITISH PHARMACOPŒIA 1932

ACETARSOL

Acetarsol

Syn.—Acetarsone; "Stovarsol".

Source.—It is 3-acetylamino-4-hydroxyphenylarsonic acid. May be prepared by the reduction of 3-nitro-4-hydroxyphenylarsonic acid and subsequent acetylation of the amino-acid thereby produced. Contains 27.0 to 27.4 p.c. As.

Characters.—A white, crystalline powder. Almost insoluble in cold water, moderately soluble in boiling water, insoluble in alcohol (95 p.c.), and in dilute acids; soluble in dilute alkalies.

B.P. Dose.—1 to 4 grs. or 0.06 to 0.25 grm.

N.B. For action and uses, *see* pages 479 and 491.

TRYPARSAMIDUM

Tryparsamide

Source.—It is sodium N-phenylglycineamide-*p*-arsonate. May be prepared by boiling an aqueous solution of sodium-*p*-aminophenylarsonate with chloracetamide, converting the resulting N-phenylglycineamide-*p*-arsonic acid into its sodium salt, and crystallising from dilute alcohol. Contains 25.1 to 25.5 p.c. of As in organic combination.

Characters.—A colourless, crystalline powder; odourless. Freely soluble in water; insoluble, or only slightly soluble in alcohol (95 p.c.), in ether, in chloroform, and in benzene.

Storage.—It should be kept in a small well-closed container, protected from light, and stored in a cool place.

B.P. Dose.—15 to 30 grs. or 1 to 2 grms., *by subcutaneous, intramuscular or intravenous injection.*

N.B. For action and uses, *see* pages 478 and 490.

ACIDUM ASCORBICUM

Ascorbic Acid

Syn.—Vitamin C.

Source.—It is the enolic form of 3-keto-*l*-gulofurano-lactone. Obtained from the ripe fruit of *Capsicum annum*, and other vegetable sources, or by synthesis. Contains not less than 98 p.c. of $C_6H_8O_6$.

Characters.—Minute colourless crystals; odourless; taste, acid, resembling that of lemon juice. Readily soluble in water; less soluble in alcohol (95 p.c.), in methyl alcohol, and in acetone.

Storage.—It is stable when kept in a glass bottle. Solution of ascorbic acid, specially if alkaline, deteriorates rapidly in contact with air.

B.P. Dose.—*Prophylactic* (daily) :—**$\frac{2}{5}$ to $\frac{4}{5}$ gr. or 0.025 to 0.05 grm.** (500 to 1000 Units). *Therapeutic* (daily) :—**$1\frac{1}{2}$ to 4 grs. or 0.1 to 0.25 grm.** (2000 to 5000 Units).

Ascorbic acid possesses antiscorbutic properties and, if tested by the *biological assay of antiscorbutic vitamin* (*vitamin C*), contains in 1 grm. 20,000 Units of antiscorbutic activity (vitamin C). See page 559.

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CALCIFEROL

Calciferol. $C_{28}H_{43}OH$

Source.—It is prepared by the ultra-violet radiation of ergosterol in a suitable solvent. The product of the irradiation, after removal of the solvent, is dissolved in alcohol (95 p.c.) or other suitable organic solvent, and strongly cooled. The unchanged ergosterol is then subjected to a complicated process of filtration, crystallisation and recrystallisation when pure crystals of calciferol are formed. (See B. P. Addendum 1936). 1 milligram contains 40,000 Units of antirachitic activity (vitamin D).

Characters.—Colourless, acicular crystals; odourless. Insoluble in water; readily soluble in alcohol (95 p.c.), in ether, in chloroform, and in acetone; soluble in 50 to 100 parts of vegetable oils.

It should be stored in hermetically sealed glass containers, from which air has been evacuated or replaced by an inert gas, protected from light, and stored in a cool place.

B.P. Dose.—*Prophylactic daily for an infant*, $\frac{1}{2400}$ **to** $\frac{1}{1200}$ **gr. or 0.025 to 0.05 mgm.** (1000 to 2000 Units). *Therapeutic daily for an infant*, $\frac{1}{1200}$ **to** $\frac{1}{800}$ **gr. or 0.05 to 0.075 mgm.** (2000 to 3000 Units).

Official Preparation

1. Liquor Calciferolis.—It is a solution of calciferol in oil. Contains in 1 grm. 3000 Units of antirachitic activity (vitamin D).

B.P. Dose.—*Prophylactic* (daily) for an infant:—**5 to 10 ms. or 0.3 to 0.6 mil** (1000 to 2000 Units). *Therapeutic* (daily) for an infant:—**10 to 15 ms. or 0.6 to 1 mil** (2000 to 3000 Units). Should be kept in a well-closed container, protected from light, and stored in a cool place. Contains 3000 units in 15 ms. or 1 mil.

PULVIS VITAMINI B_1

Adsorbate of Vitamin B_1

Adsorbate of vitamin B_1 is an adsorbate of the antineuritic vitamin (vitamin B_1) upon fuller's earth. It contains in 1 grm. 100 Units of antineuritic activity (vitamin B_1).

May be prepared from rice polishings, yeast, wheat embryo, or other suitable materials.

Characters.—A cream-coloured powder; almost odourless; tasteless. Insoluble in water, and in mineral acids.

B.P. Dose.—*Prophylactic* (*daily*) :—**15 to 30 grs. or 1 to 2 grm.** (100 to 200 Units). *Therapeutic* (*daily*) :—**30 to 90 grs. or 2 to 6 grms.** (200 to 600 Units).

OLEUM MORRHUAE

Cod-liver Oil

Source.—Obtained from the fresh liver of the cod, *Gadus morrhua*, and other species of *Gadus*, and freed from solid fat by filtration at about 0°C. It contains in 1 grm. not less than 600 Units of vitamin A activity, and not less than 85 Units of antirachitic activity (vitamin D).

Characters.—A pale yellow liquid; odour, slight, but not rancid; taste, bland or slightly fishy. Slightly soluble in alcohol (90 p.c.); miscible with ether, with chloroform, and with light petroleum.

B.P. Dose.—*Prophylactic* :—**1 to 2 mils or 15 to 30 ms.** three times daily. *Therapeutic* :—**3 to 6 mils or 45 to 90 ms.** three times daily.

N.B. This monograph replaces the monograph on Cod-liver Oil on page 561.

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ACRIFLAVINA

Acriflavine

It is a mixture of the hydrochlorides of 2 : 8-diamino-10-methylacridinium chloride and 2 : 8-diaminoacridine, and contains approximately one-third of its weight of diaminoacridine dihydrochloride. May be prepared by the partial methylation of diacetyldiaminoacridine and subsequent hydrolysis of the product with hydrochloric acid.

Characters.—An orange-red to red, crystalline powder; odourless; taste, acid. Soluble in 3 parts of water, which may be precipitated by dilution or standing; in 500 parts of normal saline solution, in alcohol (90 p.c.), and in glycerin. Insoluble in fixed oils, volatile oils and in liquid paraffin.

B.P. Dose.—$\frac{1}{2}$ to 1$\frac{1}{2}$ grs. or 0.03 to 0.1 grm.

N.B. This monograph replaces the monograph on Acriflavine on page 541.

ANTITOXINUM OEDEMATIENS

Gas-gangrene Antitoxin (œdematiens)

It is a serum, or a preparation from serum, containing the antitoxic globulins which have the specific power of neutralising the toxin formed by *Clostridium œdematiens*. Prepared by separating the serum from the blood of animals, which have been immunised by graded injections of sterile filtrate from a culture of *Clostridium œdematiens*. The serum may be used in the liquid form or may be dried. The antitoxic globulins may be obtained from the serum by fractional precipitation, and the precipitate may be used either in solution, or dried.

Characters.—The liquid serum is yellow or yellowish-brown. The solution of antitoxic globulins is yellowish-brown or greenish yellow. Both liquid forms are initially transparent, but become faintly opalescent on keeping. They are odourless with a faint odour of any antiseptic used. The solid forms are yellowish-white powders, or yellowish-brown flakes. When dissolved in 10 parts of water, they resemble the liquid forms in colour and appearance.

N. B. The label should state:—(1) whether the product is serum, dried serum, solution of antitoxic globulins, or dried antitoxic globulins; (2) the date after which it should not be used. It should also state the minimum total number of Units in the container, either in mils or grms., or the total number of mils of liquid, or grammes of dried product, in the container.

B.P. Dose.—*Prophylactic*, **20,000 Units**; *Therapeutic*, **50,000 to 100,000 Units**, by injection.

ANTITOXINUM VIBRIOSEPTICUM

Gas-gangrene Antitoxin (vibrion septique)

It is a serum, or a preparation from serum, containing the antitoxic globulins which have the specific power of neutralising the toxin formed by the *Clostridium*, commonly known as Vibrion Septique.

Characters and Preparation.—The same as other sera except that injections are made with the filtrate from a culture of the *Clostridium*, commonly known as Vibrion Septique, in a fluid medium.

B.P. Dose.—*Prophylactic*, **5000 Units**; *Therapeutic*, **10,000 to 20,000 Units**, by injection.

The uses of gas-gangrene antitoxins have been discussed on page 641. Gas-gangrene may occur from infection with three different types of organisms and the serum should be selected according to the invasion with the particular type.

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ANTITOXINUM STAPHYLOCOCCICUM

Staphylococcus Antitoxin

It is a serum, or a preparation from serum, containing the antitoxic globulins which have the specific power of neutralising the toxin formed by certain strains of *Staphylococcus*. It is prepared in the same way as other serums except that injections are made with the sterile filtrate from a culture of *Staphylococcus pyogenes* in a suitable medium.

Characters.—Same as other serums.

Labelling should be same as other sera.

B.P. Dose.—5000 to 20,000 Units, by injection.

SERUM ANTIPNEUMOCOCCICUM I

Antipneumococcic Serum (Type I)

It is a serum, or a preparation from serum, containing the immune substances which have a specific therapeutic action, when injected into persons suffering from certain diseases due to *Diplococcus pneumoniæ*.

It is prepared by separating the serum from the blood of animals, which have been immunised by graded injections of cultures of *Diplococcus pneumoniæ* (type I). The serum may be used in the liquid form or may be dried. The globulins, containing the specific immune substances, may be obtained from the serum by fractional precipitation, and the precipitate may be used either in solution or dried.

Characters.—The liquid serum is yellow or yellowish-brown. The solution of the globulins is yellowish-brown or greenish-yellow. Both liquid forms are initially transparent, but become opalescent with age. They are almost odourless, except for the odour of any antiseptic which may have been added. The solid forms are yellowish-white powders, or yellowish-brown flakes. When dissolved in 10 parts of water they resemble the liquid forms in colour and appearance.

The label should state the minimum total number of Units in the container; or the number of Units in mil or in grm., or the total number of millilitres of liquid, or grammes of dried product, in the container; and the date after which the preparation is not intended to be used.

N.B. It should not be used later then two years after the date of manufacture.

B.P. Dose.—50,000 to 150,000 Units, by *intravenous injection.*

SERUM ANTIPNEUMOCOCCICUM II

Antipneumococcus Serum (Type II).

The mode of preparation, characters, assay, storage, and doses are the same as for Antipneumococcus Serum (Type I) with the modification that suitable strains of Diplococcus pneumoniæ (type II) are used in the preparation and assay of the serum.

For action and uses of Antipneumococcus Serum, see page 644.

TOXINUM DIPHTHERICUM DETOXICATUM

Diphtheria Prophylactic

In addition to the five forms described on page 630 the following is added, viz. (*f*) **Alum Precipitated Toxoid**, a suspension of white, slightly yellow or yellowish-brown particles in a colourless liquid, prepared by treating the filtrate with formaldehyde, adding alum in

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the proportion necessary to produce a suitable precipitate, separating the precipitate, and washing and suspending it in physiological solution of sodium chloride.

ARGENTOPROTEINUM

Silver Protein

Syn.—Argentum-Proteinicum Forte; Strong Protein Silver; "Protargol."

Source.—It is a compound of silver and protein, and may be prepared by the action of a silver compound on gelatin in the presence of alkali. Contains 7.5 to 8.5 p.c. of Ag.

Characters.—A brown powder; odourless; somewhat hygroscopic. Slowly soluble in about 2 parts of water, forming a dark brown solution; almost insoluble in alcohol (90 p.c.,)

N.B. It should be kept in well-closed container, protected from light, and the solution should be dispensed in amber-coloured bottles.

The action and uses of silver protein have been described on page 117.

BISMUTHI ET SODII TARTRAS

Sodium Bismuthyl Tartrate

Syn.—Bismuth Sodium Tartrate.

Source.—May be obtained by the interaction of bismuth hydroxide and sodium acid tartrate. Contains 35 to 42 p.c. of Bi.

Characters.—A white powder, or slightly yellow scales. Soluble in less than 1 part of water.

B.P. Dose.—1 to 3 grs. or 0.06 to 0.2 grm., by *intramuscular injection.*

BISMUTHI OXYCHLORIDUM

Bismuth Oxychloride

Syn.—Bismuth Subchloride.

Source.—A basic salt of varying composition, obtained by the interaction of solutions of bismuth nitrate and sodium chloride or hydrochloric acid. Contains 79 to 81 p.c. of Bi, and not less than 12.5 p.c. of Cl.

Characters.—A white or nearly white, amorphous or finely crystalline powder; odourless; tasteless. Stable in air. Insoluble in water, soluble in dilute hydrochloric acid.

B.P. Dose.—10 to 30 grs. or 0.6 to 2 grms. *By intramuscular injection*, **1½ to 3 grs. or 0.1 to 0.2 grm.**

OFFICIAL PREPARATION

1. **Injectio Bismuthi Oxychloridi.**—Bismuth oxychloride in very fine powder, 10 grms.; dextrose, 5 grms.; cresol, 0.5 mil; sterilised water, q.s. to 100 mils. **B.P. Dose.—15 to 30 ms. or 1 to 2 mils** *by intramuscular injection.* Contains 3 grs. of bismuth oxychloride in 30 ms.

N.B. The action and uses of bismuth have been described on page 460.

CALCII CHLORIDUM HYDRATUM

Hydrated Calcium Chloride. $CaCl_2,6H_2O$

Source.—May be obtained by neutralising hydrochloric acid with calcium carbonate, and crystallising the product. Contains 98 to 102 p.c. $CaCl_2, 6H_2O$.

Characters.—Colourless crystals; odourless; taste, slightly bitter. Very deliquescent. Soluble in 0.25 part of water, and in 0.95 part of alcohol (90 p.c.).

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B.P. Dose.—*By intramuscular injection*:—1 to 3 grs. or 0.06 to 0.2 grm. *By intravenous injection*:—10 to 30 grs. or 0.6 to 2 grms.

CALCII GLUCONAS

Calcium Gluconate

It is the normal calcium salt of gluconic acid. Contains 99 to 104 p.c., of $C_{12}H_{22}O_{14},CaH_2O$.

Characters.—A white, crystalline or granular powder; odourless; tasteless. Soluble in 30 parts of water at 25°C., in about 5 parts of boiling water; insoluble in dehydrated alcohol, in ether, and in chloroform.

B.P. Dose.—30 to 60 grs. or 2 to 4 grms.

N. B. For action and uses of calcium salts, see page 93.

CHINIOFONUM

Chiniofon

Syn.—Pulvis Chiniofoni; Quinoxyl.

It is a mixture of approximately four parts by weight of 7-iodo-8-hydroxyquinoline-5-sulphonic acid and one part by weight of sodium bicarbonate. Contains 28.2 to 29.6 p.c., of I, and 18 to 22 p.c. of $NaHCO_3$.

Characters.—A light yellow powder; odourless; taste, bitter with a sweetish after-taste. Soluble with effervescence in about 25 parts of water; insoluble in alcohol (95 p.c.), in ether, and in chloroform.

Note. Solutions are decomposed by boiling.

B.P. Dose.—1 to 8 grs. or 0.06 to 0.5 grm. *By rectal injection*:—15 to 75 grs. or 1 to 5 grms.

N.B. For action of Chiniofon (Yatren) see page 491.

ERGOMETRINA

Ergometrine $C_{19}H_{23}O_2N_3$

Source.—It is an alkaloid obtained from ergot and purified by crystallisation from a suitable organic solvent.

Characters.—Colourless crystals, which become coloured on exposure to air and light; odourless; taste, slightly bitter. Soluble in water, producing a solution which shows a blue fluorescence; moderately soluble in dehydrated alcohol; sparingly soluble in chloroform.

B.P. Dose.—$\frac{1}{120}$ to $\frac{1}{60}$ gr. or 0.0005 to 0.001 grm. *By intramuscular injection*:—$\frac{1}{240}$ to $\frac{1}{120}$ gr. or 0.00025 to 0.0005 grm. *By intravenous injection*:—$\frac{1}{480}$ to $\frac{1}{240}$ gr. or 0.000125 to 0.00025 grm.

N.B.—For action and uses of Ergometrine *see* page 395.

FERRI SUBCHLORIDUM CITRATUM

Citrated Ferrous Chloride

Source.—Prepared by heating a mixture of equal volumes of hydrochloric acid and distilled water with an excess of iron, until the reaction ceases. Determine the proportion of ferrous chloride by assay. Contains not less than 68 p.c. of ferrous iron ($FeCl_2$), and not more than 5.8 p.c. of ferric iron ($FeCl_3$).

Characters.—A buff-coloured powder; taste, acid, metallic and astringent. Almost completely soluble in 1 part of water; readily in dilute mineral acids.

B.P. Dose.—3 to 5 grs. or 0.2 to 0.3 grm. (contains in 5 grs. about 1½ grs. of iron).

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HISTAMINAE PHOSPHAS ACIDUS

Histamine Acid Phosphate $C_5H_9N_3,2H_3PO_4$

Syn.—Histaminæ Phosphas.

It is the di-acid phosphate of an organic base, histamine, 4-β-aminoethylglyoxaline. Prepared by the action of phosphoric acid on histamine.

Characters.—Colourless crystals; odourless. Soluble in 4.5 parts of water; slightly soluble in alcohol (90 p.c.).

B.P. Dose.—$\frac{1}{120}$ to $\frac{1}{60}$ **gr. or 0.0005 to 0.001 grm.**

For action and uses, see page 394.

MERSALYLUM

Mersalyl

Syn.—"Salyrgan".

Is the sodium salt of salicyl-(γ-hydroxymercuri-β-methoxypropyl)-amide-O-acetic acid. Prepared by the action of mercuric acetate and methyl alcohol on salicylallylamide-O-acetic acid, and subsequent conversion to the sodium salt. Contains 2.5 to 2.8 p.c. of N, and 38.5 to 40.5 p.c. of Hg.

Characters.—A white powder; odourless; taste, bitter. Deliquescent. Soluble in about 1 part of water, and in about 3 parts of alcohol (95 p.c.).

Official Preparation

1. **Injectio Mersalyli.**—Mersalyl, 10 grms.; theophylline, 5 grms.; sodium hydroxide, 0.05 grm.; sterilised water, q.s. to 100 mils. **B.P. Dose.—8 to 30 ms. or 0.5 to 2 mils.** Contains about 3 grs. of mersalyl, and about $1\frac{1}{2}$ gr. of theophylline in 30 ms.

OLEUM IODISATUM

Iodised Oil

Iodised oil is an iodine addition product of poppy-seed oil, and may be prepared by treating poppy-seed oil with hydriodic acid. Contains 39 to 41 p.c., of combined iodine.

Characters.—A colourless or pale-yellow, clear, viscous, oily liquid; odour, slightly alliaceous; taste, bland and oily. On exposure to air and sunlight, it decomposes and develops a dark brown colour. Insoluble in water; soluble in ether, in chloroform, and in light petroleum.

It should be kept in a well-filled container, protected from light.

Uses.—Iodised oil in the form of Lipiodol is used for taking X-ray photographs of the bronchi, etc., *see* page 629.

LIQUOR IODI AQUOSUS

Aqueous Solution of Iodine

Syn.—Lugol's Solution; Liquor Iodi Compositus.

Contains iodine, 50 grms.; potassium iodide, 100 grms.; distilled water, q.s. to 1000 mils Contains $\frac{1}{20}$ gr. of iodine, and about 2 grs. of total iodine, free and combined. in 15 ms.

B.P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

SODII THIOSULPHAS

Sodium Thiosulphate. $Na_2S_2O_3,5H_2O$

Source.—May be prepared by the action of sulphur on sodium sulphite.

Characters.—Colourless, transparent, monoclinic, prismatic crystals; odourless; taste, saline. Efflorescent in warm dry air; slightly deliquescent in moist air. Soluble in 0.5 part of water at 25°C.; insoluble in alcohol (95 p.c).

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B.P. Dose.—5 to 15 grs. or 0.3 to 1 grm. *by subcutaneous, intramuscular* or *intravenous injection.*

For action and uses, *see* page 64.

THEOPHYLLINA

Theophylline. $C_7H_8O_2N_4,H_2O$

It is 1.3 dimethylxanthine, an alkaloid obtained from the dried leaves of *Camellia sinensis,* or may be prepared synthetically.

Characters.—A white, crystalline powder ; odourless ; taste, bitter. Soluble in 120 parts of water at 25°C., more in hot water ; soluble in 80 parts of alcohol (45 p.c.).

Enters into the preparation of Injection of Mersalyl.

EXTRACTUM STRAMONII LIQUIDUM

Liquid Extract of Stramonium

Prepared by percolating moderately coarse powder of stramonium 1000 grms. in alcohol (45 p.c.) q.s. to contain 0.25 p.c. w/v of the alkaloids of stramonium, calculated as hyoscyamine. It contains $\frac{1}{120}$ gr. of the alkaloids of stramonium, calculated as hyoscyamine, in 3 ms.

B.P. Dose.—½ to 3 ms. or 0.03 to 0.2 mil.

Enters into.—The preparation of Tr. Stramonii.

EXTRACTUM STRAMONII SICCUM

Dry Extract of Stramonium

Prepared by percolating moderately coarse powder of stramonium 1000 grms. in alcohol (95 p.c.) q.s. and starch to make a dry extract containing 1 p.c. of the alkaloids, calculated as hyoscyamine. 8 grs. contain about $\frac{8}{100}$ gr. of the alkaloids of stramonium calculated as hyoscyamine.

It should be kept in a small wide-mouthed, well-closed container, and stored in a cool place.

B.P. Dose.—¼ to 1 gr. or 0.015 to 0.06 grm. *In post-encephalitic and similar conditions* **:—1 to 8 grs. or 0.06 to 0.5 grm.**

The doses of the following have been altered :—

Infusum Sennæ Concentratum.—2 to 8 mils. or 30 to 120 ms.
Cinchophenum.—0.3 to 0.6 grm. or 5 to 10 grs.
Ferri et Ammonii Citras.— 1.3 to 2.6 grm. or 20 to 40 grs.

ADDITIONS TO THE B. P. 1932

Acetarsol
Acidum Ascorbicum
Antitoxinum Œdematiens
Antitoxinum Staphylococcicum
Antitoxinum Vibriosepticum
Argentoproteinum
Bismuthi et Sodii Tartras
Bismuthi Oxychloridum
Calciferol
Calcii Chloridum Hydratum
Calcii Gluconas
Ergometrina
Extractum Stramonii Liquidum
Extractum Stramonii Siccum
Ferri Subchloridum Citratum
Histaminæ Phosphas Acidus
Injectio Bismuthi Oxychloridi
Injectio Mersalyli
Liquor Calciferolis
Liquor Iodi Aquosus
Mersalylum
Oleum Iodisatum
Pulvis Vitaminis B_1
Serum Antipneumococcicum I
Serum Antipneumococcicum II
Sodii Thiosulphas
Theophyllina
Tryparsamidum

Delete monograph on Liquor Ergosterolis Irradiati, page 560.

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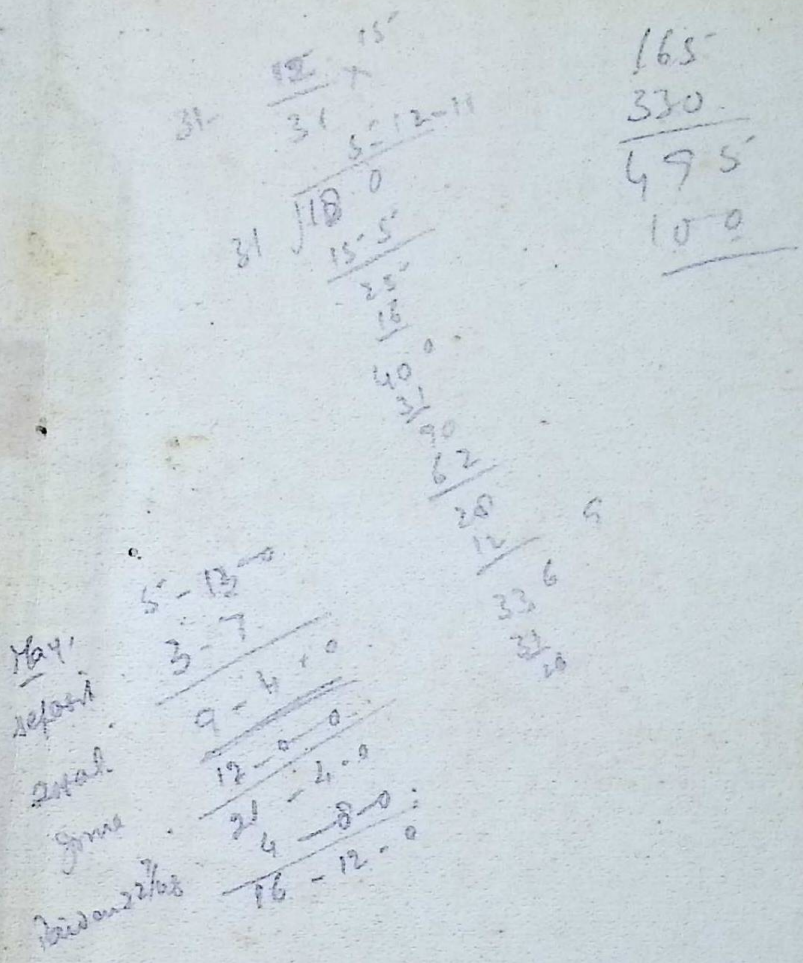

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